The American Journal of Medicine



September 1955

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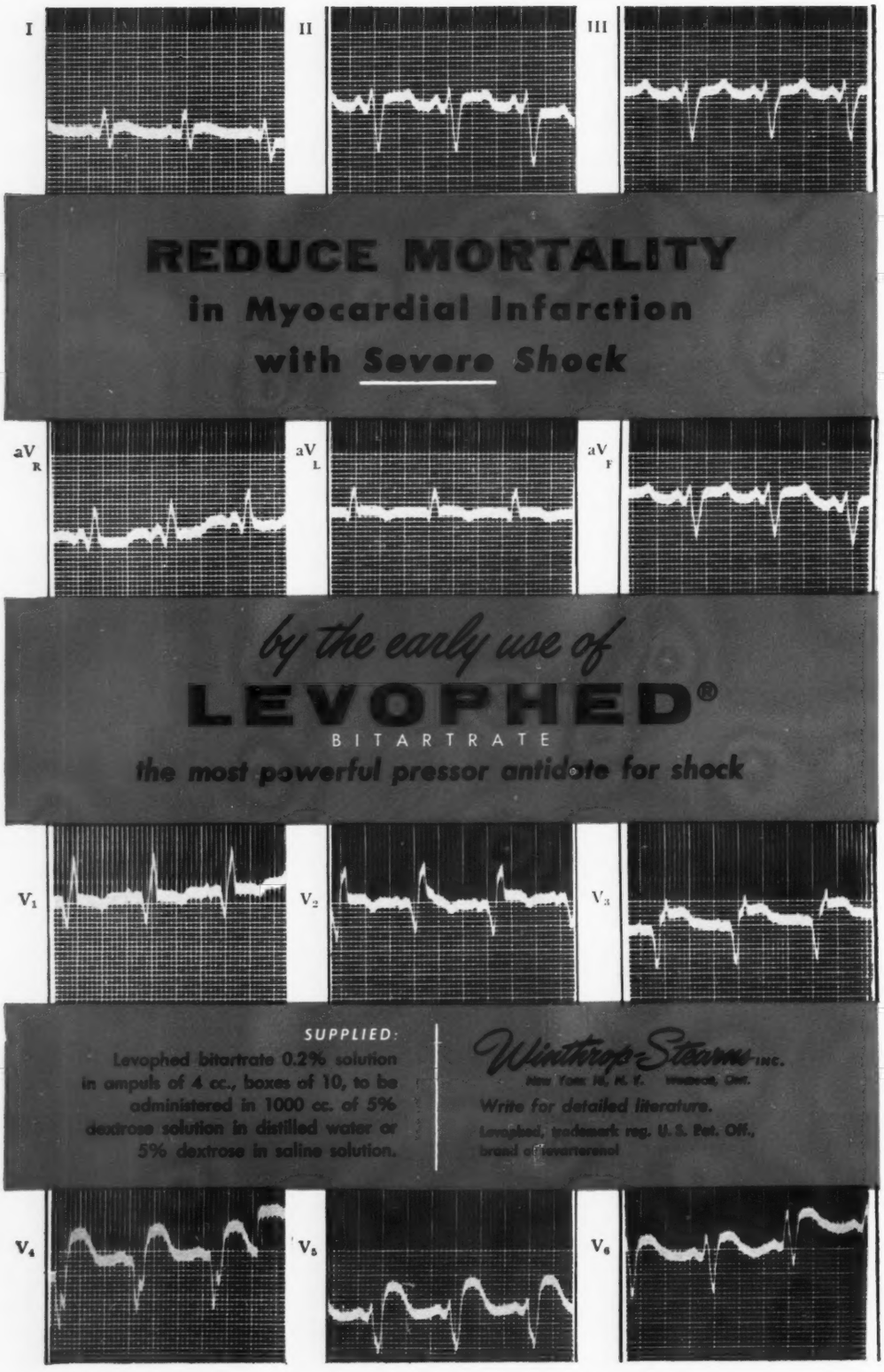
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Editorial

"For Breath Too Is Nutriment" . . . . . GEORGE R. MENEELY 323

Clinical Studies

Houssay Phenomenon in Man . . JOHN COLLINS HARVEY AND JOHAN DE KLERK 327

The authors review eleven previously recorded cases and add three of their own of rapid amelioration of diabetes associated with the development of pituitary insufficiency (the Houssay phenomenon). This startling occurrence introduces new complications, such as hypoglycemic symptoms, exquisite sensitiveness to insulin, and manifestations of thyroid, adrenal and gonadal deficiencies. Obviously, failure to appreciate the sequence of events may lead to disaster, hence the practical importance of this fascinating aspect of diabetes mellitus.

Biochemical Alterations during Steroid Hormone Therapy of Advanced Breast Cancer
B. J. KENNEDY, IRA T. NATHANSON, DOROTHY M. TIBBETTS AND JOSEPH C. AUB 337

The authors have made a careful study of serum calcium, inorganic phosphorus, alkaline and acid phosphatase, etc., in patients with advanced cancer of the breast before and during steroid hormone therapy. The results confirm and extend previous investigations of this kind, indicating the usefulness and limitations of these measurements in detecting skeletal and/or hepatic metastases. The biochemical changes accompanying steroid therapy appear to be significant enough to serve as a useful guide in evaluating tumor response.

Pathogenesis of Anemia in Patients with Carcinoma
GEORGE A. HYMAN AND JANE E. HARVEY 350

A general pattern of pathogenesis of anemia in patients with carcinoma and related disorders is becoming apparent: cryptogenic hemolysis usually not revealed by ordinary laboratory examinations but disclosed by the more refined modern technics, and normal or even increased erythropoiesis which is not, however, capable of maintaining normal red cell or iron concentrations in the blood. The present detailed study brings these points out clearly.

Metastatic Tumors of the Heart
HARVEY S. GASSMAN, RUSSELL MEADOWS, JR. AND LYLE A. BAKER 357

An analysis of the clinical and postmortem findings in 217 patients with secondary tumors of the heart, with discussion of the relevant literature.

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Association of Gastrointestinal Carcinoid Tumor with Cardiovascular Abnormalities
DAVID M. SPAIN 366

This study confirms and extends previous work indicating that the association of cardiovascular abnormalities with carcinoid tumors of the gastrointestinal tract is more frequent than can be explained by mere coincidence. The prevalence of what appears to be acquired lesions of the tricuspid and pulmonic valves and of the adjacent endocardium further suggests that more than the association of developmental anomalies may be involved. Some speculations on this point are offered.

Dermatomyositis: Diagnostic Features and Therapeutic Pitfalls
CAPT. C. A. DOMZALSKI AND LIEUT. V. C. MORGAN 370

The authors define dermatomyositis as characterized by polymyositis with creatinuria, dermatitis and edema. Two cases are described, one perhaps debatable. An excellent discussion of the literature follows, with special emphasis on the clinical and laboratory features, differential diagnosis, etiology and management. The diagnostic value of the finding of creatinuria is stressed.

Whipple's Disease . . . . . ROBERT H. PUITE AND HENRY TESLUK 383

The authors describe four new cases of Whipple's disease, two in brothers whose mother may also have had the disorder. This is the first mention of familial occurrence and raises the question of genetic transmission, possibly of a metabolic error resulting in a defect in intestinal absorption—a suggestion as plausible as anything yet proposed. In diagnosis, the authors insist upon the accumulation in macrophages of material taking the periodic acid Schiff stain and point out that such material often can be identified in peripheral node biopsies. This may obviate the need for laparotomy in some cases.

Evidence for Serologic Hyper-reactivity in Sarcoidosis
MAJOR JAMES H. SANDS, MAJOR PAUL P. PALMER, CAPT. ROBERT L. MAYOCK AND CAPT. WILLIAM P. CREGER 401

Using the mismatched blood technic, the authors show that the isoagglutinin titers obtained in patients with sarcoidosis are significantly higher than in normal or tuberculous subjects. This indication of serologic hyper-reactivity in sarcoidosis is in contrast to previously established cutaneous hyporeactivity to non-specific antigens. Another paradox of a paradoxic disease!

Contents continued on page 7

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Review

Histoplasmosis

FREDERIC N. SILVERMAN, JAN SCHWARZ, M. EUGENE LAHEY AND ROBERT P. CARSON 410

This authoritative review of the available information on histoplasmosis, based upon extensive personal experience with the disease, rounds out the present picture of the disorder and puts it into nosologic perspective. After considering the epidemiology, geographical distribution and mycology of histoplasmosis, there is extended discussion of the protean pathologic and clinical manifestations of the disease, and of the serologic and radiologic criteria of diagnosis, notably of the place of histoplasmin in diagnosis. The present status of management is then summarized. Detailed case reports are appended for graphic illustration of specific points in the main body of the review. Altogether an enlightening and instructive contribution to this controversial subject.

Seminars on Carbohydrate Metabolism

Spontaneous Hypoglycemia . . . JEROME W. CONN AND HOLBROOKE S. SELTZER 460

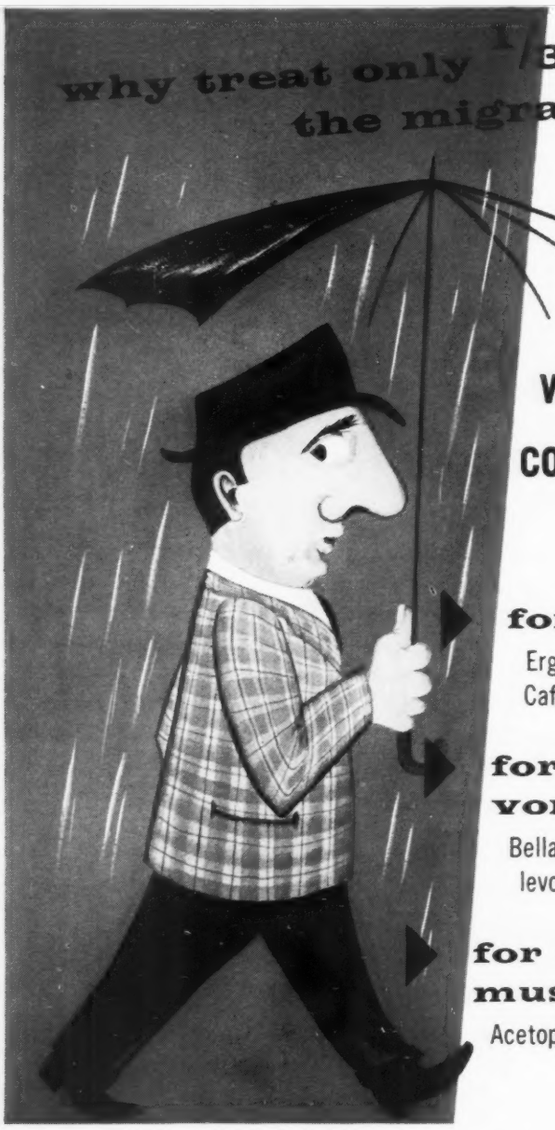
In this timely and authoritative review of the intriguing clinical aspects of spontaneous hypoglycemia the authors properly begin by defining the term and describing its symptomatic manifestations. They next offer an up-to-date classification based on etiologic factors and indicate how these several factors may be determined in the individual case. The three most frequent categories —functional hyperinsulinism, organic hyperinsulinism and hepatogenic hypoglycemia—are then considered in some detail, with illustrative case reports. A discussion of some of the rarer causes of spontaneous hypoglycemia concludes the presentation.

Clinico-pathologic Conference

Jaundice and Ascites with Recovery for Two Years; Recurrence of Jaundice, with Abdominal Pain, Hematemesis and Azotemia 479

Clinico-pathologic Conference (Washington University School of Medicine).

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Case Report

Subacute Bacterial Endocarditis Due to Listeria Monocytogenes
PAUL D. HOEPRICH AND HYMAN M. CHERNOFF 488

A case of subacute bacterial endocarditis of unusual interest, apparently the first recorded in man to be due to Listeria monocytogenes and the first human Listeria infection with unequivocal agglutinin levels in the serum.

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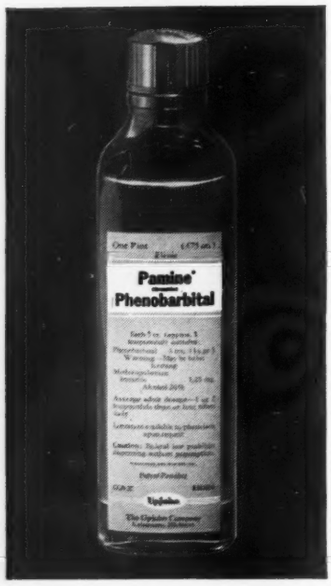
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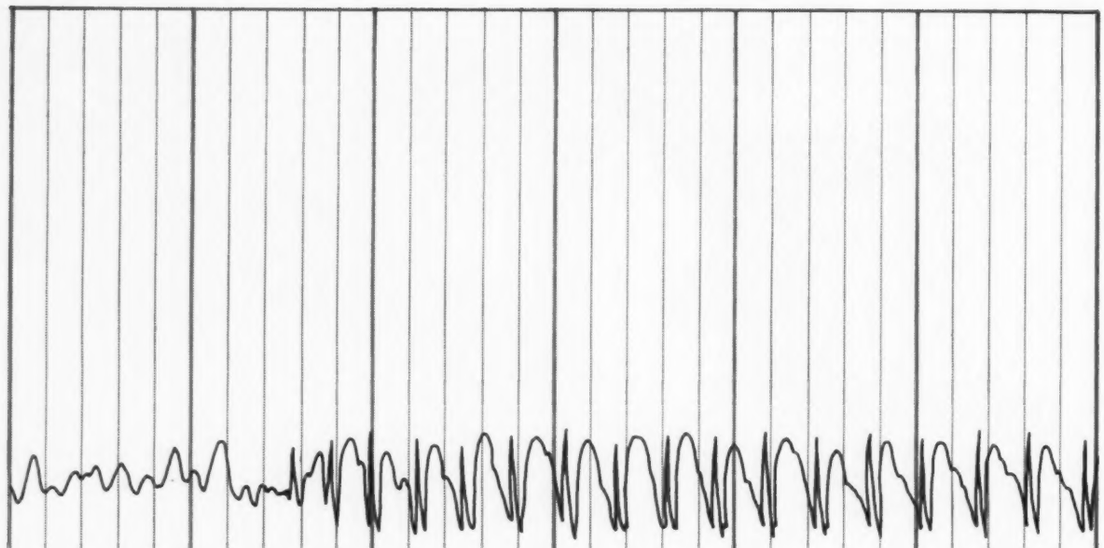
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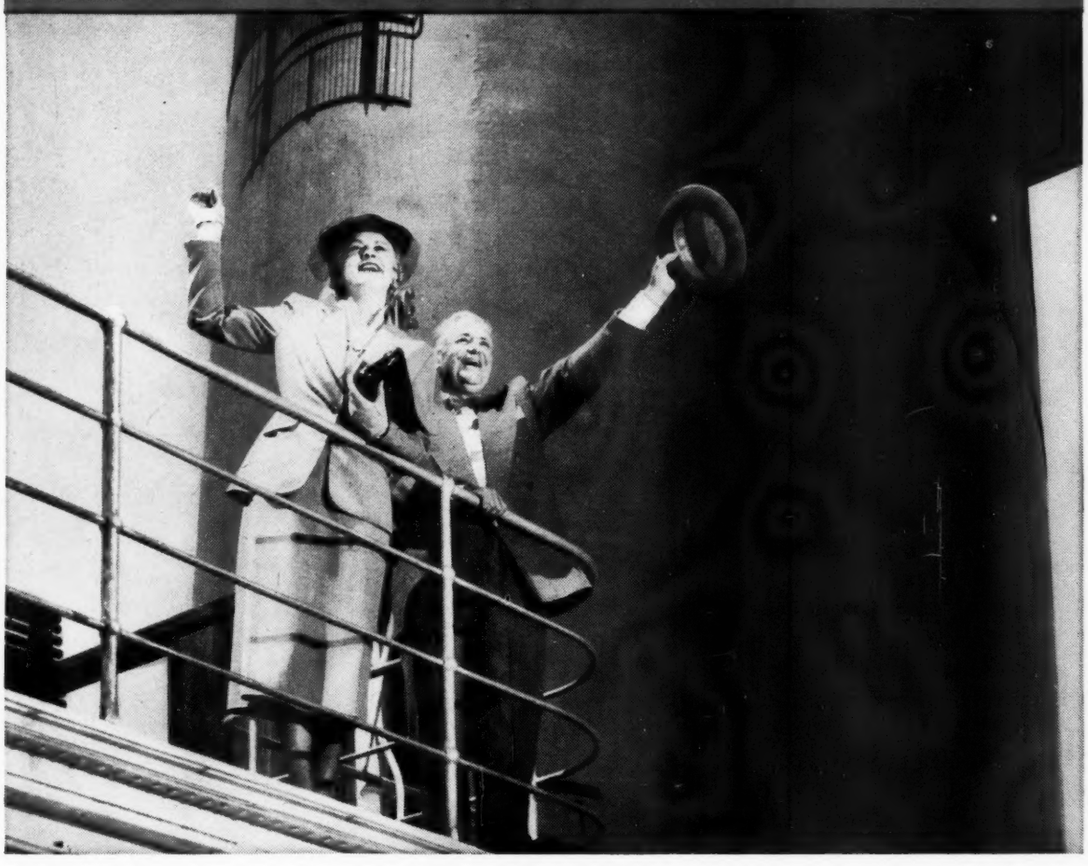
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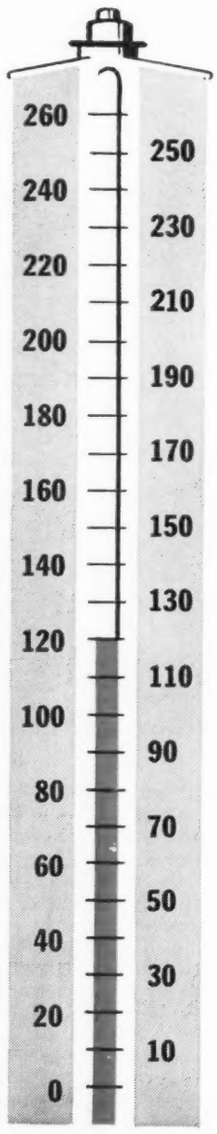
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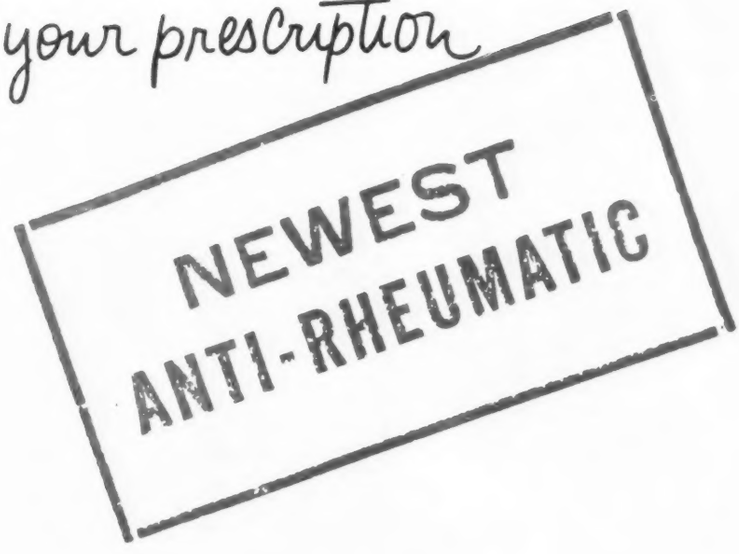
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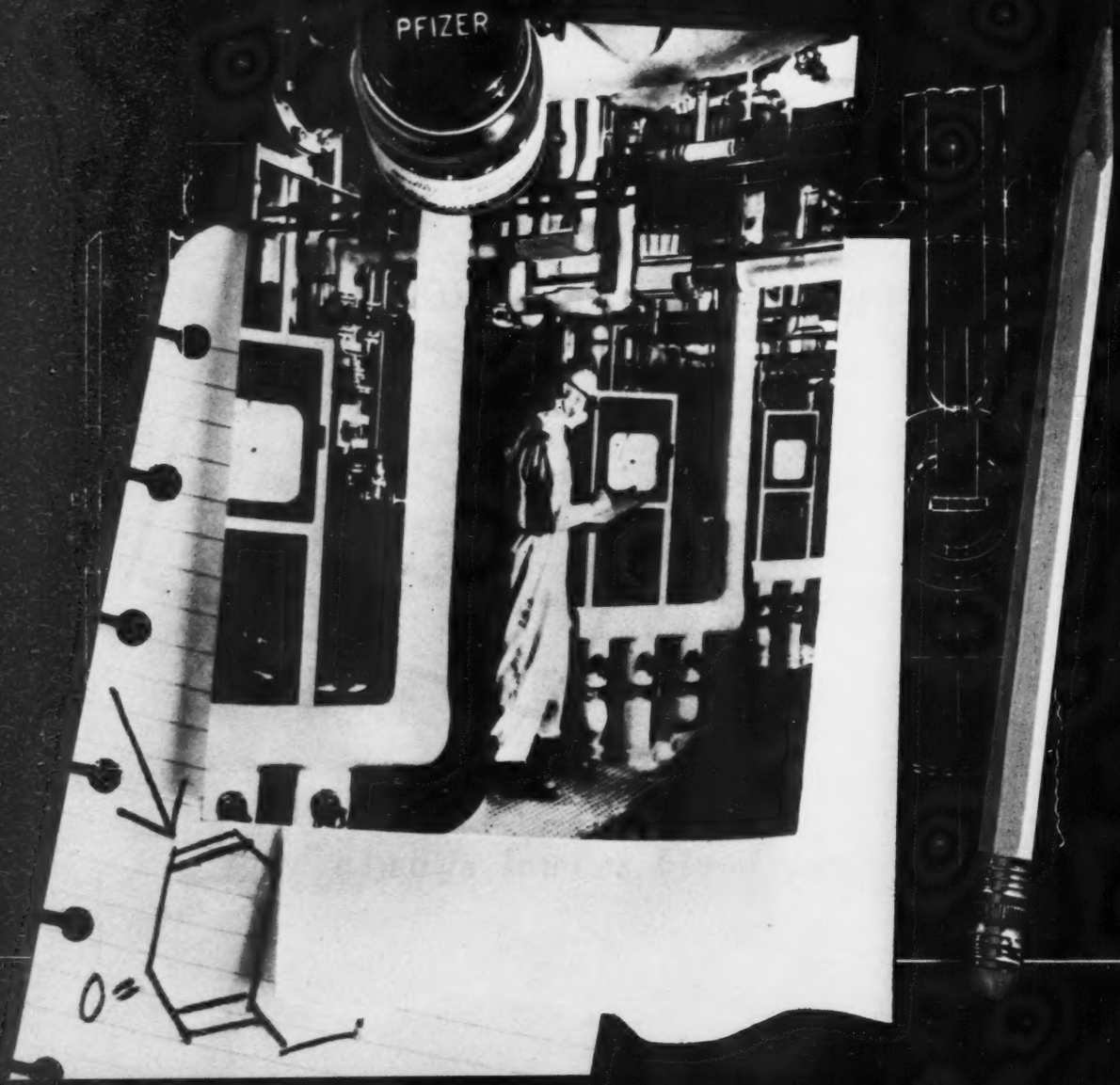
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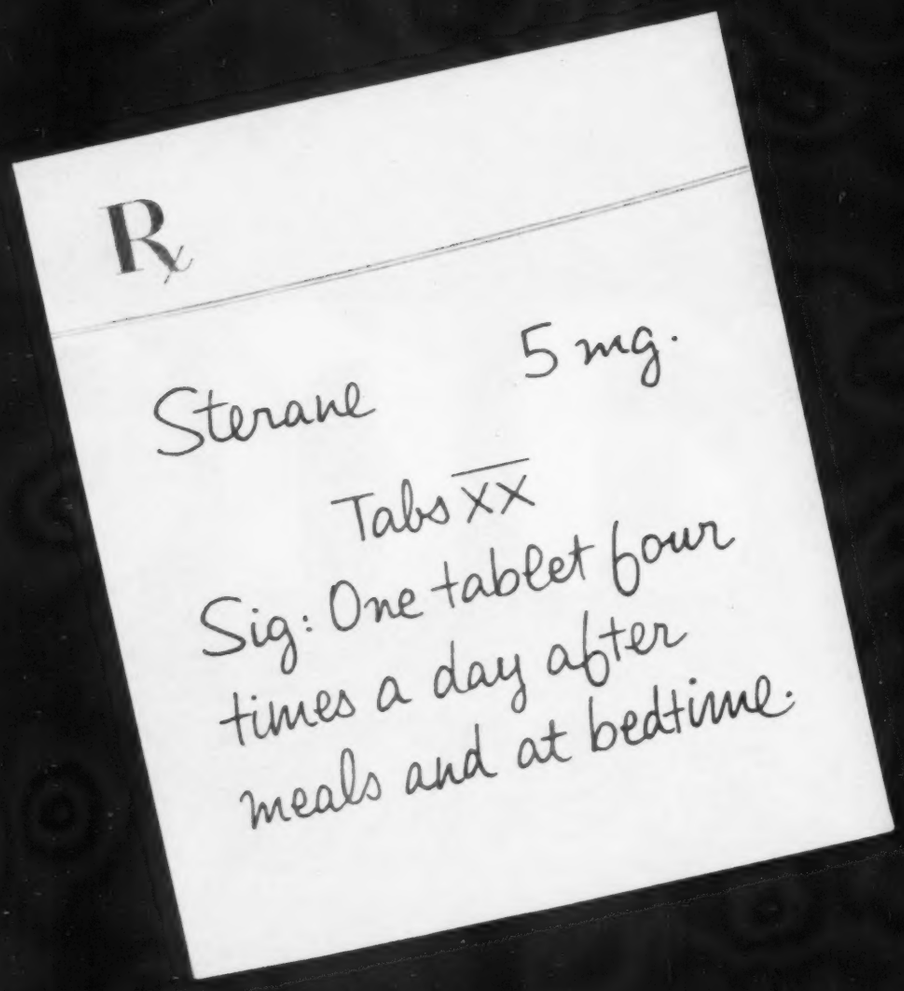
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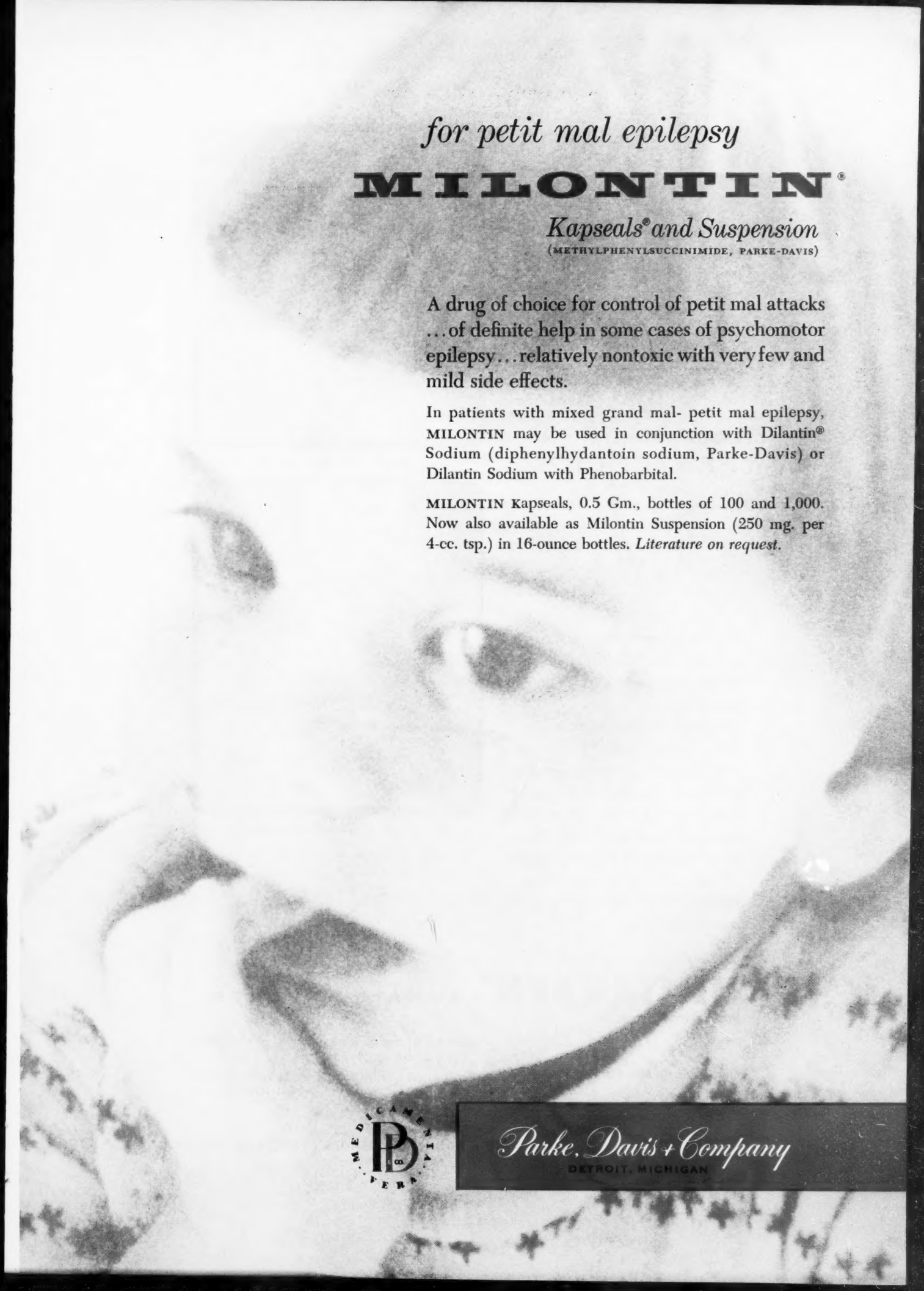
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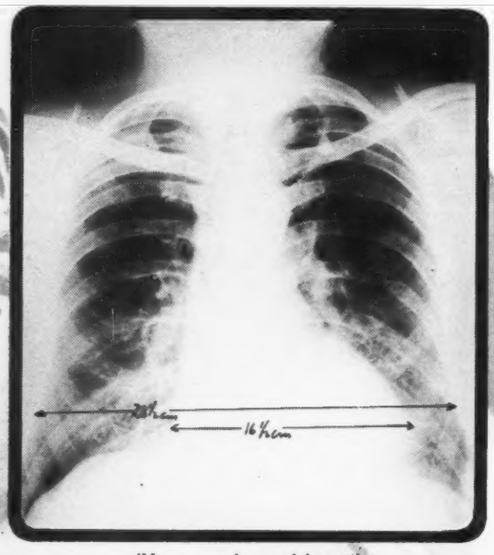
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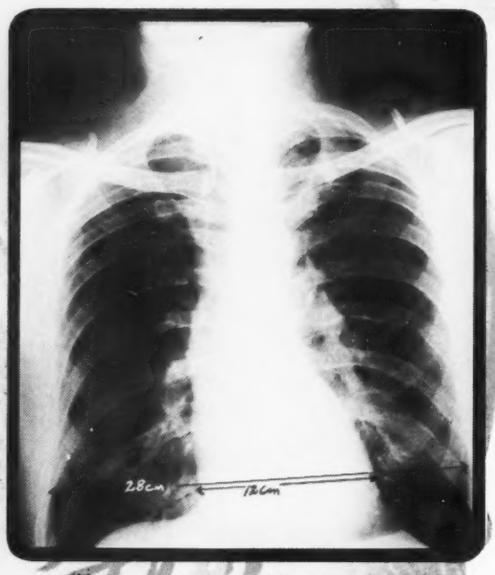
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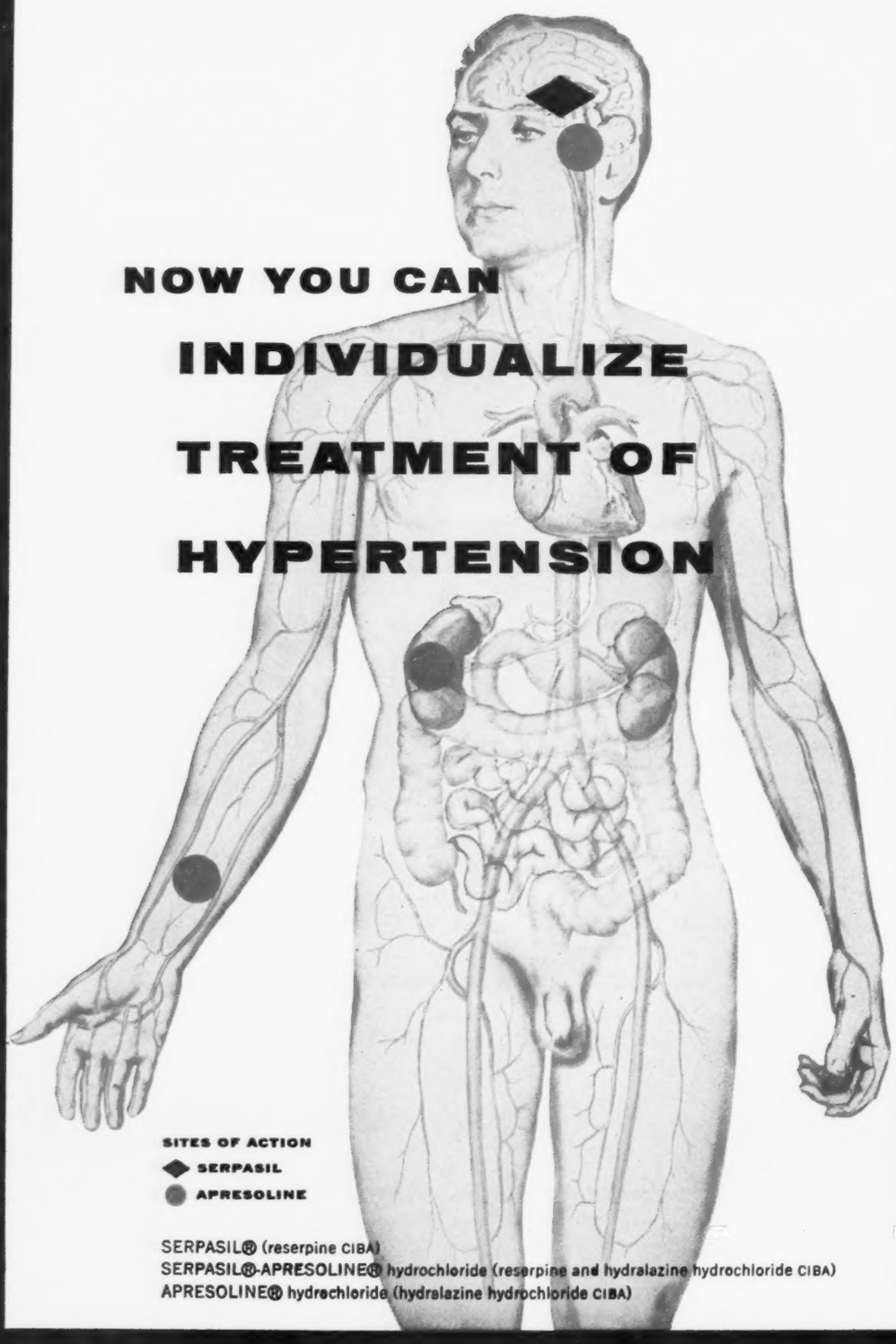
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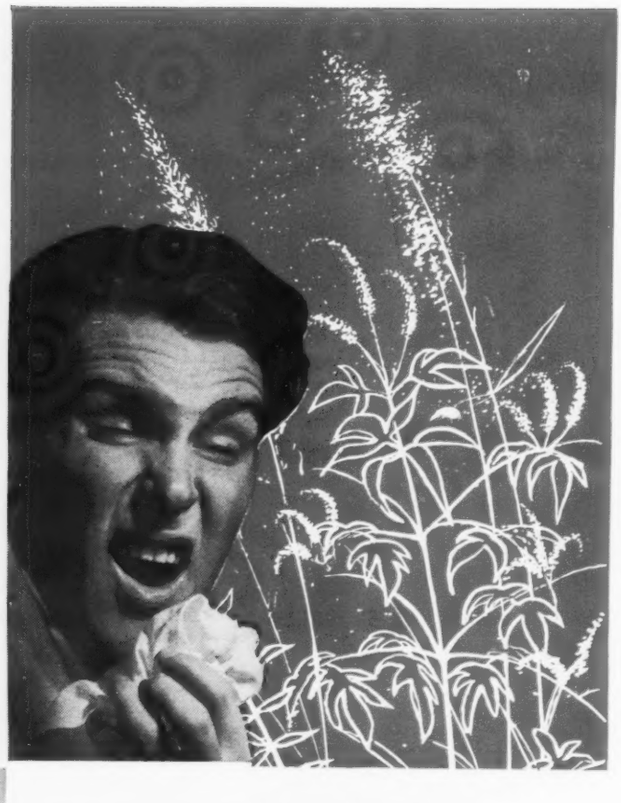
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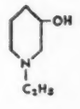
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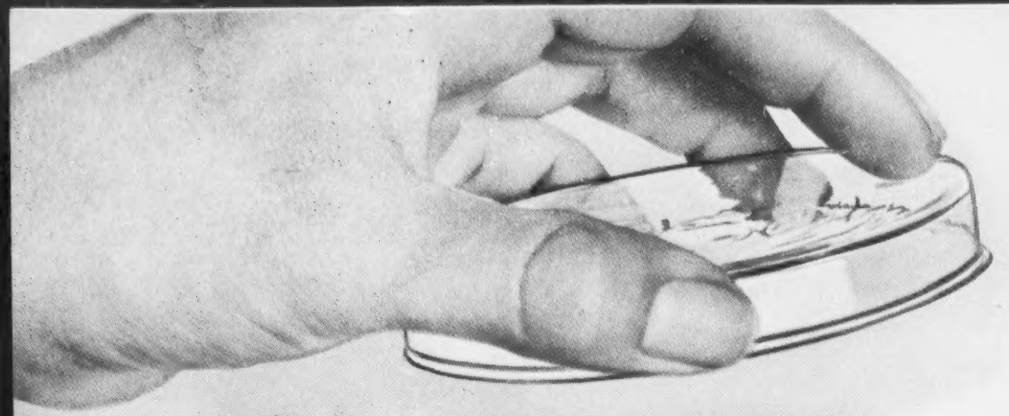
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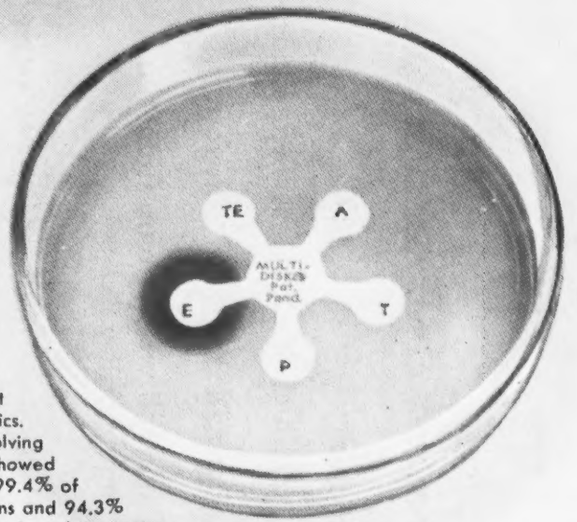
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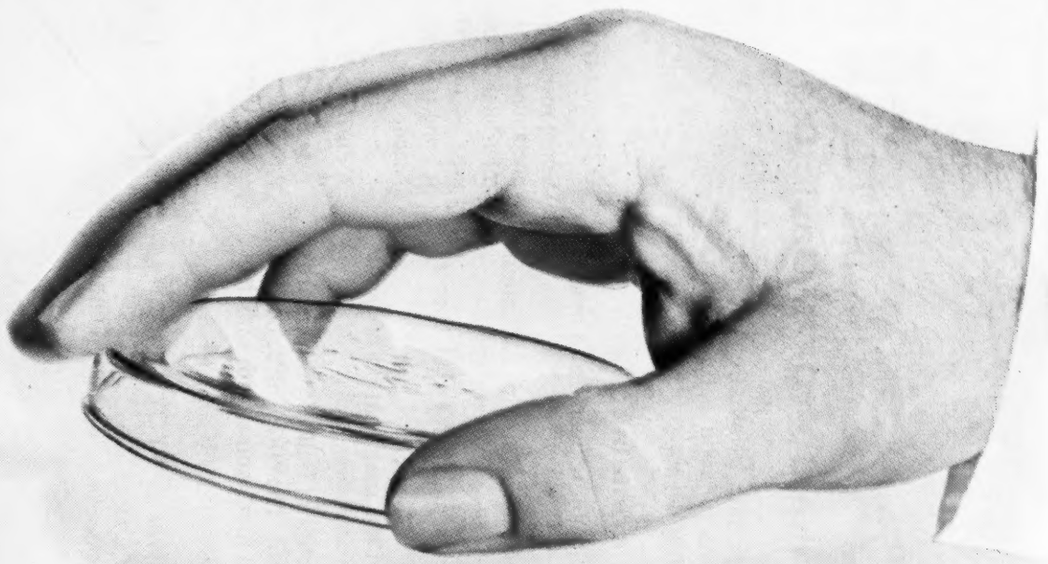
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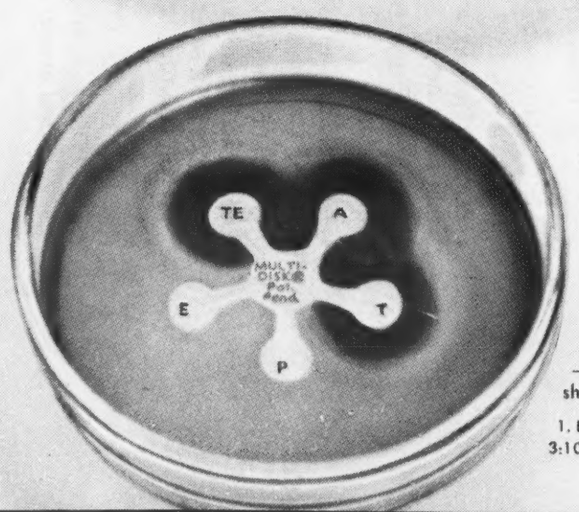
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1. Eisenberg, et al., Antib. & Chemo., 3:1026-1028, Oct., 1953.

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Semoxydrine HCl (Methamphetamine HCl) 5 mg.; Pentobarbital 20 mg.; Ascorbic acid 100 mg.; Thiamine HCl 0.5 mg.; Riboflavin 1 mg.; Niacin 5 mg.

1. Eisfelder, H. W.: Am. Pract. & Dig. Treat., 5:778 (Oct.) 1954.

2. Sebrell, W. H., Jr.: J.A.M.A., 152:42 (May) 1953.

3. Sherman, R. J., M.D.: Medical Times, 82:107 (Feb.) 1954.

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Dosage:

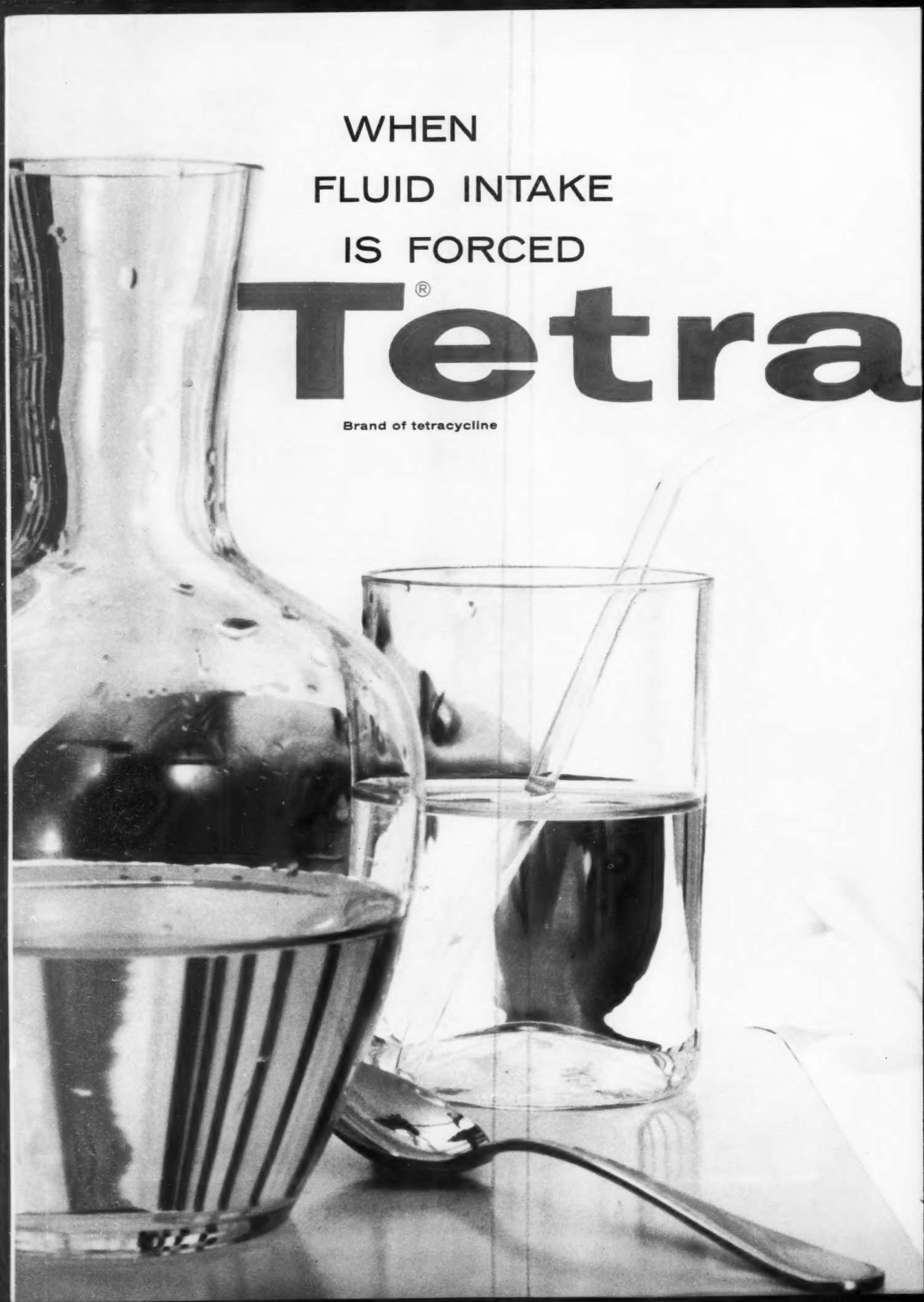
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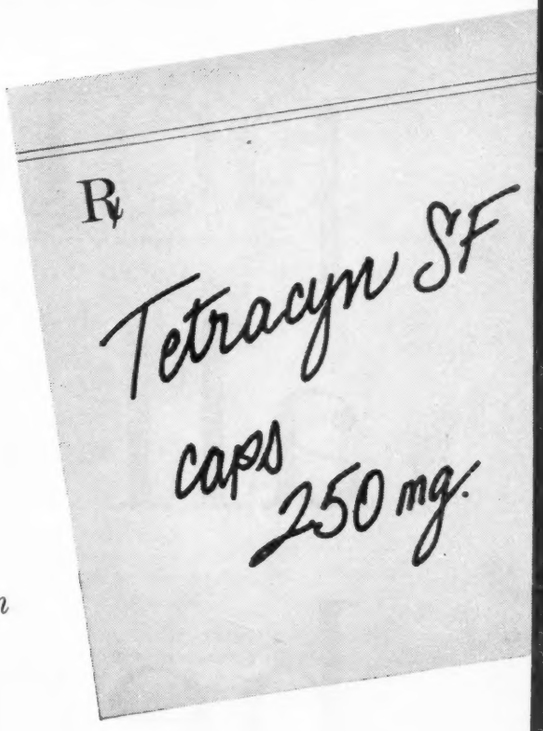
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1. Dumas, K. J.; Carlozzi, M., and Wright, W. A.: Antibiotic Med. *1*:296 (May) 1955.
2. Prigot, A.: Ann. New York Acad. Sc., in press.
3. Milberg, M. B., and Michael, M., Jr.: ibid.
4. Pollack, H., and Halpern, S. L.: Therapeutic Nutrition, Prepared in Collaboration with the Committee on Therapeutic Nutrition, Food and Nutrition Board, National Research Council, Washington, D. C., 1952.

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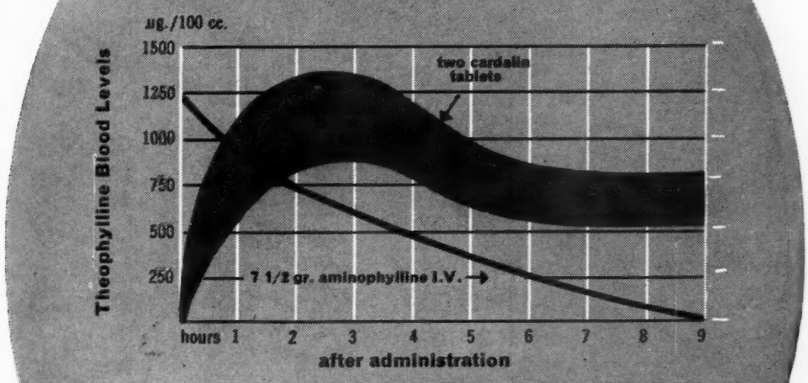
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References on the therapeutic efficacy of Cardalin

1. Segal, M. S., et al.: Quart. Rev. Allergy & Applied Immunol. 6: 399, 1952.
2. Levine, E. R.: Med. Rec. & Ann. 46: 322, 1952.
3. Segal, M. S., and Dulfano, M. J.: GP 7: 58, 1953.
4. Barach, A. L., et al.: Dis. Chest 23: 121, 1953.
5. Segal, M. S., and Dulfano, M. J.: Chronic Pulmonary Emphysema. Mod. Med. Monographs, New York, Grune & Stratton, 1953, No. 8, pp. 79-80.
6. Bickerman, H. A., et al.: Ann. Allergy 11: 309, 1953.

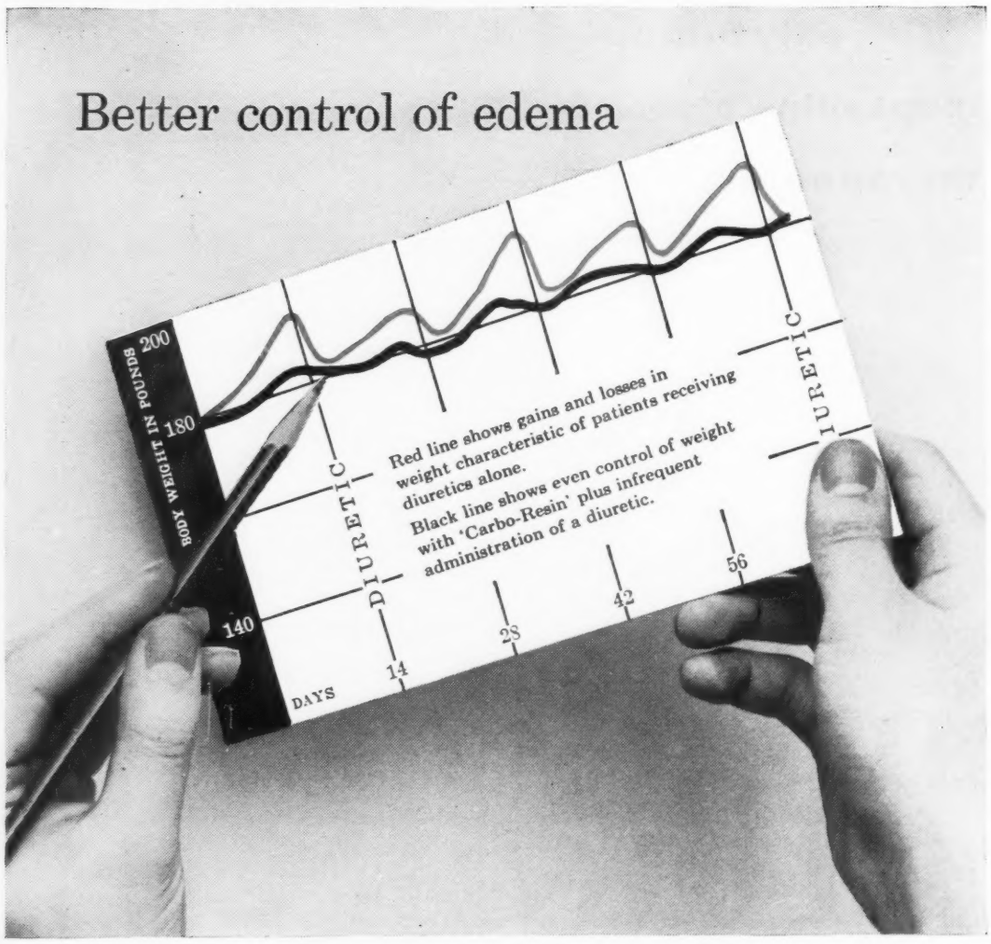
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The American Journal of Medicine

VOL. XIX SEPTEMBER, 1955 NO. 3

Editorial

"For Breath Too Is Nutriment"

WHEN we treat a patient with chronic "non-specific" pulmonary disease we often feel ourselves in a trackless quagmire of contradictory recommendations for therapy in a condition which we are ill equipped to diagnose and which, by its bewildering complexity of seemingly unconnected manifestations, paralyzes our powers. All around us, among our professional colleagues, in the current medical literature, in hospital charts and laboratory reports there is an incomprehensible chatter, a flowing alphabet soup of cryptic and code-like jargon, foreign to our ear, of M. B. C. and F. R. C. interspersed all too frequently with an algebraic expression or, worst of all, with that Indian sign to the medical mind, a differential or an integral symbol.

A congeries of factors seems to have thrust us into this slough: here are bronchodilators, there are emphysema belts, yonder aerosol generators (perhaps with design to insufflate or exsufflate), everywhere are antibiotics in bewildering profusion which might cure our patient's infection or, who knows, might turn the bronchial passages into a defenseless playground for an overgrowth of ordinarily innocuous but now slimily coalescent pathogens raised like an army of zombies from the normal microbial flora. And down the hall dwells a young scientist with burning eyes and glistening spirometers who, facile in crypto-alphabetese, would, at the twist of a stopcock, turn emphysema into fibrosis while threading a heart with nylon tubes. Not the least of our reactions is guilt. We feel we should know, that others do know, the solid from the quicksand in this swamp, and boundless anxiety issues from our neurotic guilt.

There is some justice in our view. The mire of chronic non-specific pulmonary disease is not new, and the weirdly festooned and clustered woods of pulmonary impairment have always been; but as gloom dispels in the growing light of medical science we can see the situation more vividly if not more clearly. Meanwhile the proportion between middle and older aged in the population is continually increasing, the killing diseases of childhood and youth are decreasing, so that the relative incidence and importance of the insidiously progressive chronic non-specific pulmonary diseases are multiplying. Some confusions concerning the origin of dyspnea have been resolved. In many instances the heart may be exonerated and the lungs indicted. If we erroneously diagnose failure of the former when the latter is the culprit, time will confirm us in our error because heart failure will inevitably occur as a result of pulmonary failure, if something else does not carry our patient off in the meantime. Finally, effective diagnostic and therapeutic measures have come much more plentifully to our hands. That a situation is susceptible of management imposes upon us a duty to recognize and to treat it skillfully.

Much of our self-recognized befuddlement is derived from the fact that at the time we attended medical school chronic pulmonary insufficiency was a troublesome, refractory and fortunately (in a sense) an infrequently recognized condition receiving minimal curricular attention. We feel the lack of systematic grounding in the basic principles and now, harried, we are attempting to fill the hiatus piecemeal. Perhaps it would be comforting to look to the past to see how long a path has really been

traversed and how slowly we have moved along it.

A place to start might be that " . . . earliest surviving example of observation and conclusion, the oldest known evidence of an inductive process in the history of the human mind," the Edwin Smith surgical papyrus (Breasted). This document, which dates from the sixteenth century B.C., copies a much older text. The latter, about the twenty-sixth century B.C., was in itself an annotated version of one originating, it is thought, in the Pyramid Age around the thirtieth century B.C. The instructive form directs us to examine the patient and conclude one of the following: "an ailment which I will treat"; "an ailment with which I will contend" or "an ailment not to be treated." Chronic pulmonary disease of the sort which concerns us never falls in the first category of curable illness and should not be placed in the third of hopeless illness. Chronic disabling pulmonary disease is an ailment with which the physician must "contend."

To do this we must know the natural history of the disorders we propose to manage "I hold it is an excellent thing for a physician to practice forecasting," said Hippocrates (*Prognostica*) "for if he discover and declare unaided by the side of his patients the present, the past and the future and fill in the gaps in the account given by the sick, he will be the more believed to understand the cases, so that men will confidently entrust themselves to him for treatment. Furthermore, he will carry out the treatment best if he know beforehand from the present symptoms what will take place later. . . . " Hippocrates, if he were about, would nowadays be willing to modify "unaided" to encourage recourse to the needed specialists in radiology, electrocardiography pulmonary function, bacteriology and cardiac catheterization, but would doubtless sternly insist that we remain at the patient's side to convert the specialists' information to useful plans for the patient. This we can do only through a working comprehension of these ramifications of the modern art acquired from study, if not from practice, of their technics.

Anaximenes of Miletos proposed air, pneuma, as the primary substance " . . . permeating everything" and indeed, from the biologic point of view, such is true. Every part and system of the body is permeated with air and dependent upon an endlessly refreshed supply of it for well-being. Interference with the bodily aerating equipment must of necessity manifest itself in myriad ways.

Complexity, however, cannot cause mental panic unless we allow it. A child of seven steps up to a television set and unhesitatingly tunes in a station, adjusts the horizontal and vertical raster control circuits to the locking signals of the transmitting station, focuses the electronic beam unerringly, adjusts the bias of the control grid of the cathode ray tube to a degree of apparent contrast to suit his fancy, turns the audio volume control wide open and thunders off into outer space in a reaction-engined craft without a qualm. Confronted with a circuit diagram of the set, he would blink with incomprehension, a reaction that will persist with him well into engineering school a decade and more later. There he will be taught an engineer's trick: reduce the incomprehensible whole into comprehensible parts. Here is the power supply, here its filter network, here the automatic volume control, and so on. Thus, piece by piece, the whole becomes simple. There is no scientific concept borne of the human mind which is not simple in its basic elements. To get at these basic elements may be another matter! When the work is new it is difficult to thread a way among the conflicting data, but with time and the work of many minds the findings are digested, condensed, sorted and simplified to a teachable or learnable unit of knowledge. How far we go in our studies of this subject is a purely personal matter but whatever we attempt all will be lost if we swamp ourselves in complexity instead of systematizing our attack on the problem and subdividing it into comprehensible elements. This is difficult if not impossible to do alone in a field where areas of comprehension are chequered among larger areas of ignorance.

Engineers can teach us another trick for working with systems we do not or cannot fully understand: the useful tool of the four terminal network parameters. Here an electronic device is envisaged as though two wires, the input circuit, disappeared through two terminals into a "little black box," and two wires, the output circuit, emerge through two other terminals from the opposite side. It is often entirely unnecessary to know the contents of the box; it may be enough to know what changes are produced in the output circuit by certain changes in input, and vice versa. A "little black box" can be made to contain that part of any system about which the technical details

are unknown, or as much or as little as desired. So if for a given amount of power fed into the "little black box" a lesser amount emerges, it is evident the loss occurred within the box, while if there is gain of power it is axiomatic that the box is playing an active role and its behavior in this respect could be characterized by a generator of appropriate properties. In either event we would want to know where the lost electricity went or where the gained energy originated, but these are questions for the research laboratory.

The "little black box" will serve very well for the bedside. It has to be accepted definitely that we cannot understand everything. As researchers open one by one the "little black boxes" and show their contents to us, more and more unopened boxes are revealed. It is poor research indeed which does not raise more ghosts than it lays. We may conveniently place such matters which we do not understand into useful "little black boxes." Thus we can make intelligent use of the knowledge that the volume of air moved by the bellows action of the lung during maximal voluntary hyperventilation increased 20 per cent following administration to the patient of a bronchodilator drug to lead us to the conclusion that bronchoconstriction is a factor in our patient's malady despite a limited comprehension of all the complex mechanisms involved. Such reasoning should not be adduced as an excuse for unnecessary ignorance but rather as a working technic with what knowledge has been allowed us.

Empedocles of Agrigentum, he of the four elements, fire, air, water and earth, who flourished early in the fifth century B.C., performed a crucial experiment which proved the corporeality of air. By plugging the hole in one end of a clepsydra (a hollow vessel with holes at each end) with his finger and immersing the vessel in water he showed that the entrapped air prevented the entrance of water until he removed his finger from the top hole and let the air escape. Not much of vital interest to physiologists was added to this information about air until 1668 A.D., some twenty-one centuries later.

The Hippocratic physicians were close observers of the respiratory movements. Thus the second case described in *Epidemics* I: "from the beginning the breath in this case was throughout rare and large." Hyperpnea, we may suppose, since the clinical picture described is dehydration and metabolic acidosis in a patient dying of acute fever with copious diarrhea. Again, Cheyne (1818) and Stokes (1846) were antedated in their observations of the kind of breathing which commonly bears their names by the author of Case 15 in *Epidemics* III: "Respirations rare and large with long intervals becoming afterwards short."

The forty-eighth chapter of *De Alimento*, an aphoristic work of the Hippocratic corpus of uncertain authorship written about the turn of the fifth century B.C., which is taken as the text for this editorial, shows the preoccupation of this school with the way of breathing and the "obscure sybylline" utterances they were forced to take refuge in because of the lack of real comprehension of respiration. To recognize air as a "food," Sarton points out, could only then have been a guess or a metaphor. The point was not proved until Priestley in 1772 rediscovered Mayow's "igneo-aerial" spirit which he isolated as oxygen, and Lavoisier soon afterwards disposed of the phlogiston theory setting the matter straight for all time.

Bewilderment about the purpose of respiration persisted for centuries despite the fact that it was known to the earliest Egyptians, even to their paleolithic predecessors, that air was essential to life. Murder by suffocation is not a new invention, and execution by entombment (and consequent suffocation) did not begin with Aida. Jelliffe traces the more recent developments: Galen thought respiration was for the purpose of cooling the heart and this doctrine persisted until recent times. Harvey recognized the existence of "two different currents" of the blood but supposed one to generate the vital spirit in the left side of the heart, the other to get rid of the foul vapors and the heat of the innate fire burning in the heart. Von Helmont recognized the existence of "fixed air" (carbon dioxide) from his studies on fermentation but had no idea what it was, and the concept was lost. Borelli elaborated upon the concept of the bellows action of the chest and with others through the seventeenth century clarified the mechanics of respiration, coupling in the observations of Malpighi on the minute structure of the lung and advancing finally to the point of recognizing that the "particles" of air enter into and become mixed with the blood. Hooke also proved the necessity of air for life by experiments in artificial respiration, and Lower "by his careful transfusion experiments demonstrated that the difference between dark venous blood and lighter arterial blood was due to the admix-

ture of air thus explaining the color change which had been recorded for thousands of years and referred to thousands of causes."

John Mayow in 1668 cracked the problem left for him by Empedocles two thousand years before proving that air, while indeed it had corporeality, was not a single substance.* "Not all of the air was used by the lungs in influencing the blood but only a certain part of it, and although he called it by a different name (*spiritus nitro-aerius*) it was that part now known as oxygen." He saw that respiration was a process " . . . analogous to combustion, that both fire and breathing removed from air the *igneoaerial* particles" (Foster). Stephen Hales first stated the principle of free and combined gases and Joseph Black rediscovered Von Helmont's "fixed air," the carbon dioxide given off by the lung. When, after a hundred years of forgetfulness of Mayow's work, Priestley and Lavoisier, as earlier mentioned, elaborated upon the elements of external gaseous respiration, it remained only for Gustavus Magnus, just a century ago, to prove the presence of the gases in different proportions in the blood and thus complete "the last chapter in the unraveling of this secret of nature." The stage was set for the great advances in pulmonary physiology, especially in its quantitative aspects, made over the last century.

Unfortunately the original literature on chronic pulmonary disease is enormous. In one segment of the field alone, pulmonary function testing, over seven hundred authors during the last two decades have published articles which have attracted enough attention to be quoted one or more times in other papers. The leading articles have been disseminated for the most part among forty-three different journals without much concentration in any particular one. Just in the last two decades have reviews, texts and, most useful, organized postgraduate courses on the subject begun to appear. Widespread use of Roentgen diagnosis, the advent of practical tests of pulmonary function, the ready availability of effective antibiotics and effective therapeutic products of synthetic chemistry, particularly bronchodilators, all within our clinical lifetime is bringing us nearer comprehension of that mystical but inspired passage: "Pulsations of veins and breathing of the lungs according to age, harmonious and unharmonious, signs of disease and of health, and of health more than disease, and of disease more than health. For breath too is nutriment."

GEORGE R. MENEELY, M.D.
Veterans Administration Hospital
Nashville, Tennessee

* Some credit Robert Boyle or Robert Hooke with this discovery.

Clinical Studies

The Houssay Phenomenon in Man*

JOHN COLLINS HARVEY, M.D. *and* JOHAN DE KLERK, M.D.†
Baltimore, Maryland

RECENTLY two patients with diabetes mellitus have been encountered in whom there was rapid amelioration of diabetes, and insulin administration was discontinued. One patient, still alive, has generalized sarcoidosis, and signs of pituitary insufficiency appeared concomitantly with disappearance of the signs of diabetes; the other patient died suddenly and an abscess of the pituitary gland was found at autopsy. Another case of "disappearing" diabetes, in association with infarction of the pituitary, was brought to our attention by Dr. Frank Ford. Since individuals with panhypopituitarism can now be returned to a more or less normal state of health by judicious hormonal replacement therapy,[1] it is imperative to recognize pituitary insufficiency when it occurs. If insulin administration be continued in the diabetic who develops panhypopituitarism, severe hypoglycemia may occur and death may follow quickly; but if the panhypopituitarism be recognized, proper treatment allows continued life. Pituitary insufficiency should be considered immediately in the diabetic if the requirement for insulin decreases very rapidly, or if insulin shock occurs with great frequency and hypoglycemia is prolonged and relatively resistant to the administration of intravenous glucose.

The three cases to be described are instances of such an occurrence.

CASE REPORTS

CASE 1. P. H. (Johns Hopkins Hospital No. 160105), a twenty-two year old white diabetic, was in the ninth month of her first pregnancy when she entered the hospital on the Obstetrical Service in December, 1938. She had had headaches of progressive severity for one month, frequent insulin shocks and edema of the legs. There was no familial history of diabetes. Diabetes developed when the patient was thirteen years old, and because of its severity 70 units of crystalline insulin daily had been prescribed by her physician in addition to dietary regulation. Dietary indiscretions were frequent, as well as omissions of insulin administration; the patient was treated for severe diabetic acidosis on several occasions. Frequently she had episodes of insulin shock when she omitted one or two meals. There were always promptly relieved by administration of glucose intravenously. During pregnancy, the diet was largely uncontrolled and the diabetes was managed by her physician only with great difficulty.

Five weeks before admission malaise developed followed in a week by the sudden onset of severe headaches, anorexia and generalized weakness. Generalized anasarca then developed. During this time insulin shock occurred often and usually at night. In the attacks occurring during the week before admission the patient was observed to have generalized convulsions. Insulin dosage was reduced but hypoglycemic episodes occurred. On admission she appeared ill. There was tachycardia and tachypnea. She was weak and drowsy. There was generalized edema. Flame-shaped hemorrhages were seen in the left retina. Blood pressure was 112/70 mm. Hg. in the recumbent position. A viable infant estimated to weigh 2,600 gm. could be palpated on abdominal examination.

The patient was kept at bed rest. Despite careful dietary control and cautious administration of crystalline insulin in small amounts, hypoglycemic episodes were frequent. Blood sugar levels measured at these times varied from 40 mg. per cent to 65 mg. per cent. On her fourth hospital day she was spontaneously delivered of a stillborn infant. Blood loss during delivery was measured at 250 cc. Immediately following this

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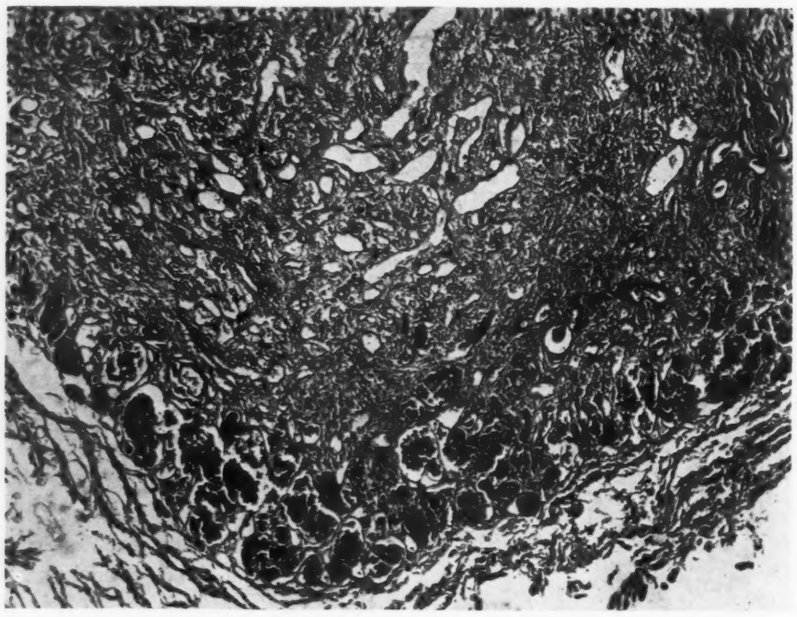


FIG. 1. Section of the pituitary showing extreme destruction and scarring; × 66.

severe hypoglycemic shock occurred which was relieved by intravenous glucose administration. The patient had a sharp rise in temperature to 105°F. From this time until her death two and a half weeks later there was intermittent fever. Hypoglycemic episodes occurred usually at night and blood sugar levels were always found to be between 37 and 65 mg. per cent, although insulin administration had been stopped before delivery. These episodes were accompanied with left-sided fits; they appeared to be made worse by prolonged fast. The patient was weak, listless and anorectic. Glucose was administered intravenously in the last days of life as well as aqueous adrenal-cortical extract. The patient fell into a deep coma six days before death. She never regained consciousness despite glucose administration. It was thought irreversible changes had occurred in the brain as a result of the episodes of profound hypoglycemia. She died quietly three weeks after admission. A diagnosis* of infarction of the pituitary was made and it was suggested that the amelioration of the diabetes mellitus and the subsequent hypoglycemia were secondary to this.

At autopsy she was found to have in addition to low grade endometritis and cystitis, atrophy of the pancreas, hyalinization of the islets of Langerhans, extreme destruction and scarring of the hypophysis secondary to infarction, (Fig. 1) and atrophy of the adrenal cortex. The infarction of the pituitary was estimated to be of two months' duration.

CASE II. G. R. (J. H. H. No. 272744), a sixty-eight year old retired white carpenter, entered the Urological Service of the hospital on October 25, 1952, for a perineal prostatectomy for benign prostatic hypertrophy. There was a strong familial history of diabetes mellitus. He had been found to be a diabetic at the age of fifty-eight years and had been followed in the Diabetic Clinic of the hospital for four years. Regulation was accomplished by attempted dietary control and administration of insulin. In the past he had had one severe bout of acidosis apparently precipitated by severe infection. Before operation, while he was in the hospital receiving a 1,600 calorie diet and 20 units of protamine zinc insulin every morning, several blood sugar determinations, made when he was fasting, were between 140 and 240 mg. per cent. Glycosuria was always present, but without acetonuria. Perineal prostatectomy was performed successfully. On the second postoperative day he had several shaking chills and became febrile. The patient was given penicillin and streptomycin. Fever disappeared within two days. Crepitation and foul-smelling drainage appeared at the operative site on the fifth postoperative day. The diabetes became difficult to control. Blood sugar level rose to between 220 and 320 mg. per cent. He became mildly

*Made by Dr. James Bordley, III, then Resident Physician.

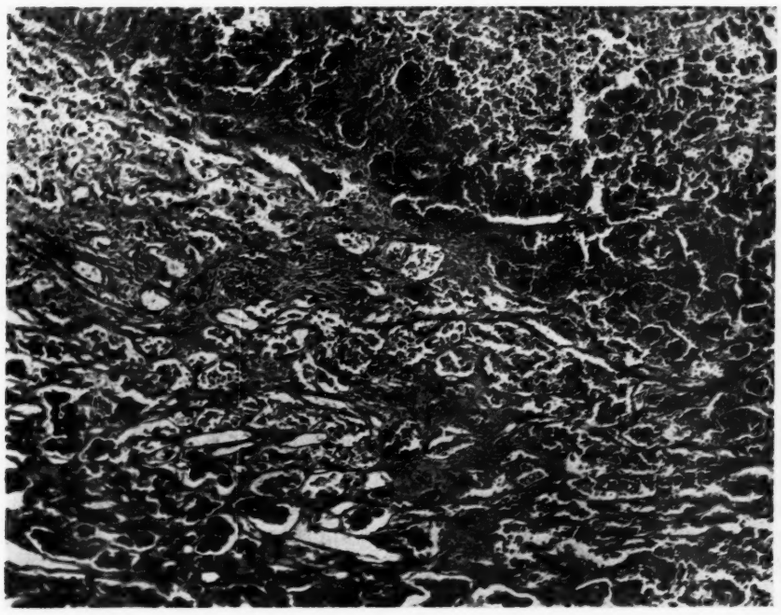


FIG. 2. Section of the pituitary showing abscess formation and necrosis in the anterior lobe; × 66.

acidotic. Insulin dosage was increased from 20 to 55 units of protamine zinc insulin every morning, but glycosuria persisted and blood sugar levels remained high. Streptococcus faecalis and a group D beta hemolytic streptococcus were cultured from the perineal drainage. With antibiotic therapy the fever and tachycardia disappeared and the fasting blood sugar levels returned to normal on the eleventh postoperative day. Insulin dosage was decreased from 55 to 10 units of protamine zinc insulin every morning. Blood sugar levels fell below normal and insulin administration was discontinued on the fourteenth postoperative day; glycosuria never reappeared. Low grade fever returned. On the sixteenth postoperative day the patient complained of mild headache, ocular pain and photophobia. This increased in severity for the next four days. Fever, tachycardia and tachypnea reappeared. The patient became weak and listless; anorexia increased and vomiting occurred. Examination of the eye grounds showed slight pallor of the discs and slight fullness of the retinal veins. On the twentieth postoperative day the patient became comatose. A varying neurologic pattern appeared with generalized flaccidity, twitching of the facial and pectoral muscles, absent deep tendon reflexes and unsustained bilateral ankle clonus. It was thought this picture represented extreme hypoglycemia and, after blood was obtained for a sugar determination, 100 gm. of glucose was administered intravenously in a 10 per cent solution, but the patient died four hours later. The blood sugar concentration was subsequently found to be 32 mg. per cent.

At autopsy in addition to generalized arteriosclerosis, atrophy of the pancreas and hyalinization of the islands of Langerhans, there was abscess formation at the operative site in the perineum and abscess and necrosis of the anterior lobe of the hypophysis. (Fig. 2.) Str. faecalis was cultured from the abscesses in the pituitary and in the perineum.

CASE III. A. M. (J. H. H. No. 533662), a forty year old Negro laborer, was last in the hospital in April, 1953. There was a strong family history of diabetes mellitus but of no other endocrine disorders. The patient had syphilis at the age of fifteen years. This was treated with penicillin during his first hospital admission in 1950.

In 1949 he was admitted to another hospital in severe diabetic acidosis. He had had symptoms of diabetes for the preceding six months. The diabetes was well controlled by dietary regulation and insulin administration, 50 units of protamine zinc insulin and 30 units of crystalline insulin every day. During that hospital stay he had an excruciating headache lasting for several days. There were no abnormal physical findings associated with this. Following discharge he took insulin sporadically. He first appeared at

The Johns Hopkins Hospital in 1950. At the Wilmer Ophthalmological Institute he was found to have interstitial keratitis, iritis, lymphadenopathy and hepatomegaly. There were no visual field defects. Biopsy of an axillary gland showed lesions compatible with the diagnosis of sarcoid. The blood sugar determinations obtained when the patient was fasting were all normal and the oral glucose tolerance test was normal. He had stopped taking insulin and had given up dieting some six months previously. At no time was there glycosuria. Several determinations of the basal metabolic rate yielded results of approximately −30 per cent of normal. The serum concentrations of sodium, potassium and chloride were always normal. There was mild normochromic-normocytic anemia, and a hypoplastic bone marrow. X-ray of the sella turcica showed it to be intact and at the upper limits of normal in size.

The patient left the hospital but returned again in February, 1953, complaining of weakness, dizziness, crampy abdominal pain and watery diarrhea. Anorexia was prominent although there was no nausea or vomiting. On physical examination he was found to have low grade fever and mild hypotension. Blood pressure was 90/60 mm. Hg, recumbent. He appeared lethargic and chronically ill. The skin was dry and scaly. No increase in pigmentation was noted. Facial, axillary and pubic hair was sparse. There was generalized lymphadenopathy. The liver was palpable at the costal margin. The testes were moderately atrophied. Determinations of blood sugar levels made when the patient was fasting were always normal and the oral glucose tolerance curve was flat, but the intravenous glucose tolerance curve was diabetic in type. The severe normochromic-normocytic anemia discovered during his first admission in 1950 was again noted. The protein-bound iodine was 2.4 μg./100 cc. of serum.* 17-Ketosteroid levels in the urine were 2.2 mg./24 hours and 1.0 mg./24 hours on two occasions.† Serum levels of sodium, chloride and potassium were normal. X-rays of the skull showed a normal sella. Visual fields were normal. Blood transfusions corrected the anemia. It was recommended that the patient take replacement hormonal therapy (thyroid, cortisone and testosterone) but this advice was refused. The patient continues with signs of increasing pituitary insufficiency manifested by weakness, lassitude, slow mentation, loss of hair, loss of libido, atrophy of genital organs, coarse skin, intolerance to cold, and hypotension.

He has generalized sarcoidosis and it is believed that there is involvement of the anterior lobe of the pituitary by this process. Clinically he presents a picture of pituitary insufficiency of moderate degree. The amelioration of the diabetes is thought to be the result of the pituitary insufficiency.

* Normal value: 4.0 to 8.0 μg./100 cc. of serum.

† Normal value for males of this age: 8.0 mg./24 hours to 14.0 mg./24 hours.

DISCUSSION

In 1930 Houssay and Biasotti reported that the diabetes produced by extirpation of the pancreas in toads could temporarily be prevented or its severity diminished by removal of the pituitary gland.[2] In 1931 they reported that in dogs diabetes mellitus produced by extirpation of the pancreas could be ameliorated by removal of the anterior lobe of the pituitary; in addition they found that such dogs were hypersensitive to insulin and that brief fasting caused severe hypoglycemia.[3] Other investigators have confirmed these findings in other mammals, amphibians, reptiles and fishes.[4] The glucose tolerance curves in such animal preparations may remain diabetic in type.[5] In 1937 Young reported that large amounts of pituitary extract given to dogs over a prolonged period of time produced permanent diabetes.[6] The pancreases of these diabetic dogs showed either degranulation and hyalinization of the beta cells alone or hyalinization of all islet tissue.[7] Gaebler and Galbraith found that in dogs rendered diabetic by pancreatectomy, but well controlled by insulin administration, anterior pituitary extract caused worsening of the diabetic state and made control difficult.[8]

In 1940 Gemmill showed that rat diaphragm incubated in a glucose-containing medium led to more substantial glycogen deposition in the diaphragm when insulin was present than when insulin was absent.[9] Using this technic Stadie and his co-workers found that the ease with which insulin combines with the tissue is impaired in the diaphragm of rats injected with crude anterior pituitary extract or purified growth hormone before sacrifice.[10] Nelson independently has made the same observation.[11] Price, Cori and Colowick reported that the addition of anterior pituitary extract to extracts

of rat tissues produced inhibition of the hexokinase activity of these tissues, and that when insulin was added to this reaction, the inhibition was counteracted.[12] Whether the action of anterior pituitary extract is through inhibition of hexokinase activity is not certain for Stadie and Haugaard[13] could not confirm this experiment of Price et al.

Whatever the exact mechanism, it is abundantly clear that there is a mutual antagonism between the effects of insulin and an anterior pituitary hormone upon the concentration of blood glucose in the animal body. It is not surprising then to find this same antagonism in man,[14,15] with amelioration of diabetes in diabetic individuals who develop anterior pituitary insufficiency. Although Calder[16] is usually given credit for reporting the first instance in man in 1932, Balo[17] had reported two such cases in 1924. Since then eleven cases of amelioration of diabetes associated with spontaneous destruction of the anterior pituitary gland have been reported in the literature,[18–28] also two cases of amelioration of diabetes after the anterior pituitary gland had been removed surgically.[29,30] These reports are summarized in Tables I and II.

Spontaneous pituitary insufficiency and amelioration of diabetes has shown no sex predilection. It has occurred in both juvenile and senile patients with diabetes mellitus. Of the reported cases five were males and six were females. Five individuals were under thirty. In the cases reported in this communication two were males, aged forty and sixty-eight years, respectively, and one was a female aged twenty-two years.

The duration of diabetes before the development of the pituitary insufficiency in the previously reported cases varied from four months to twenty-one years. The majority had had diabetes for at least four years. In the three cases reported here the diabetes had been present five, nine and ten years before any signs of the pituitary lesion developed.

Among the six females reported in the literature, the pituitary insufficiency occurred concomitantly with pregnancy or with postpartum hemorrhage in four. In the one female reported in this communication the pituitary lesion developed during pregnancy.

The complaint common to all of the patients reported here and in several of the previously reported cases was severe headache. In retrospect this complaint was made at the time infarction must have occurred in the pituitary. Attacks of hypoglycemia quickly followed and were usually not initially recognized as attacks of hypoglycemia. They were ushered in by delirium, fits or coma. Rapidly changing neurologic signs conforming to no set pattern appeared in all cases. Because of these prominent neurologic signs attention was usually focused on the central nervous system. Generally, a low level of the blood sugar was a surprising incidental finding. When hypoglycemia was discovered its full significance was usually unappreciated. Despite reduction in insulin dosage, hypoglycemia attacks usually continued. Within seven to ten days most patients had discontinued insulin completely. Despite this, glycosuria did not appear except when large amounts of glucose were given intravenously. In all patients the manifestations of hypoglycemia were profound and the symptoms were quite refractory to treatment with intravenously administered glucose. Moreover, hypoglycemia quickly recurred when the intravenous administration of glucose was stopped.

Of the eleven previously reported cases nine of the patients have died and have come to autopsy. In eight massive infarction of the pituitary gland secondary to thrombosis of its nutrient arteries was found. Death occurred in these eight patients as early as a week or as late as six months after hypoglycemic attacks began. In the ninth case (Case 3, Table I) death occurred twelve years after the onset of hypoglycemic attacks. When the first hypoglycemic attacks occurred, the patient was thought to have a pituitary tumor. X-rays of the skull then showed "definite evidence of a pituitary tumor—an abnormally dense deposit lying in the sella—and a lateral stereo confirmed the position of the radio-opaque mass." Insulin was no longer required. Three years later glycosuria and hyperglycemia recurred and administration of insulin was again required in increasing dosages. The patient lived nine years longer, requiring up to 30 units of crystalline insulin every day. He finally died in diabetic coma. At autopsy there was no sign grossly of pituitary enlargement or tumor and microscopically the gland was normal.[19]

Of the three cases reported in this communication two have come to autopsy. The female had anterior pituitary infarction; she lived only six weeks after attacks began. The male had an abscess destroying the pituitary gland, metastatic

TABLE I

AMELIORATION OF DIABETES MELLITUS FOLLOWING SPONTANEOUS DEVELOPMENT OF PITUITARY INSUFFICIENCY
(SUMMARY OF PREVIOUSLY REPORTED CASES)

Case No., Author and Year Reported	Age and Sex	Pregnancy	Duration Diabetes (Yr.)	Duration Development Pituitary Insufficiency	Headache Presenting Complaint	Signs of Pituitary Insufficiency								Decrease in Insulin Requirement	Glucose Tolerance Curves after Pituitary Insufficiency	Antemortem Diagnosis	Hormonal Replacement Therapy	Fate	Autopsy Findings			
						Weakness	Lassitude	Lowered Blood Pressure	Hair Loss	Atrophy Genital Organs	Breast Atrophy	Signs of Hypothyroidism	Hypoglycemia						Infarction Anterior Pituitary	Hyalinization Islet Tissue	Adrenal-cortical Atrophy	Other
1. Balo, 1924	16♂	.....	3	2½ mo.	0	..	?	?	..	..	..	..	+	.....	Not done	No	None	Died 2½ mo. after onset hypoglycemic attacks	+	+	+	Pulmonary Tbc
2. Balo, 1924	28♀	No	1½	1 mo.	0	..	?	?	..	..	..	..	+	.....	Not done	No	None	Died 1 mo. after onset of hypoglycemic attacks	+	+	+	Pulmonary Tbc
3. Lyall and Innes, 1933	27♂	.....	⅓	2 mo.	0	+	+	+	+	+	..	0	+	30 U ↓ 0 U	Remained diabetic	Yes	Anterior pituitary extract infrequently	Lived 12 yr.; 3 yr. after pituitary insufficiency appeared, diabetes reappeared; patient died in diabetic acidosis	No (normal pituitary)	+	No	.....
4. Kotte and Vanderache, 1940	40♂	.....	5	2 wk.	+	+	+	+	0	0	..	0	+	? ↓ 0 U	Not done	No	None	Died suddenly in profound hypoglycemia 12 hr. after hospital admission	+	+	+	Pulmonary Tbc
5. Feldman, Susselman, Roberts and Lipitz, 1947	50♀	No	12	wk.	+	+	+	+	+	+	+	0	+	No insulin taken at any time	Not done	Yes (Simmonds' disease)	Adrenocortical extract daily	Died 4 mo. after onset of symptoms in profound hypoglycemia	+	+	+	.....
6. Vanderbroech and Ferin, 1947	35♀	Yes	5	6 mo.	+	+	+	+	+	+	+	+	+	60 U ↓ 40 U	.....	Yes (Sheehans' disease)	Gonadotrophins weekly	Alive but ill; replacement therapy not satisfactory	.....	..	.....	.....
7. Marzullo and Handlesman. 1951	53♂	.....	1½	2 wk.	+	+	+	+	0	+	+	..	+	165 U ↓ 20 U	Remained diabetic	No (? Addison's disease)	Desoxycorticosterone acetate daily to death	Died 6 wk. after onset of hypoglycemic attacks	+	+	+	.....
8. Williams, 1952	27♀	Yes	4	16 days	0	+	+	+	0	0	0	0	+	60 U ↓ 0 U	Not done	No	None	Died 16 days after hypoglycemic attacks began in profound hypoglycemia resistant to I.V. glucose therapy	+	+	+	.....

TABLE 1 (*Continued*)

Case No., Author and Year Reported	Age and Sex	Pregnancy	Duration Diabetes (Yr.)	Duration Development Pituitary Insufficiency	Headache Presenting Complaint	Signs of Pituitary Insufficiency								Decrease in Insulin Requirement	Glucose Tolerance Curves after Pituitary Insufficiency	Antemortem Diagnosis	Hormonal Replacement Therapy	Fate	Autopsy Findings			
						Weakness	Lassitude	Lowered Blood Pressure	Hair Loss	Atrophy Genital Organs	Breast Atrophy	Signs of Hypothyroidism	Hypoglycemia						Infarction Anterior Pituitary	Hyalinization Islet Tissue	Adrenal-cortical Atrophy	Other
9. Israel and Conston, 1952	30♀	Yes	16	6 mo.	0	+	+	+	+	0	0	+	+	20 U ↓ 0 U	Not done	No	None	Died suddenly following cesarean section; pituitary insufficiency developed after a postpartum hemorrhage 3 yr. previously	+	+	Slight	.....
10. Poulson, 1953	38♀	Post-partum	21	6 mo.	0	+	+	+	+	+	+	+	+	30 U ↓ 8 U	Remained diabetic	Yes (Sheehan's disease)	Cortisone, insulin, thyroid extract } daily Percorten, stilbesterol } weekly	Alive and well 9 yr. after presumed postpartum necrosis of anterior pituitary; replacement therapy satisfactory	.....	..	.....	.....
11. Rothfeld and Rodas, 1954	65♂	.....	9	2 yr.	0	+	+	+	+	+	+	+	+	25 U ↓ 0 U	Remained diabetic	No	None	Insufficiency developed 2 yr. prior to admission; last 9 mo. of life symptoms became worse; rapid progression to death	+	+	+	.....

TABLE II

AMELIORATION OF DIABETES MELLITUS BY SURGICAL REMOVAL OF THE ANTERIOR PITUITARY GLAND

Case, Author and Year Reported	Age and Sex	Duration Diabetes before Hypophysectomy (yr.)	Date Hyphophysectomy	Results of Hypophysectomy				Hormonal Replacement Therapy	Fate	Autopsy
				Decrease Insulin Requirement	Hypoglycemic Episodes	Glucose Tolerance Test	Other Signs of Pituitary Insufficiency			
1. Chabanier Puech, Lobo-Onell, Lelu, 1935	22 ♂	7	Oct., 1934	Yes 170 U ↓ 70 U	Frequent	Not done	Yes	None	Died 4 mo. after operation in hypoglycemia	Absent pituitary; pulmonary tuberculosis
2. Luft and Olivecrona, 1953	30 ♂	28	Nov., 1951	Yes 80 U ↓ 12 U	None	Not done	Yes	Cortisone, doca, thyroid, testosterone	Alive and well 2 yr. after operation	
3. Luft and Olivecrona, 1953	20 ♀	14	May, 1952	Died postoperatively						
4. Luft and Olivecrona, 1953	28 ♀	17	May, 1952	Died postoperatively						
5. Luft and Olivecrona, 1953	24 ♀	14	June, 1952	Yes 60 U ↓ 8 U	Yes	Not done	Yes	Cortisone, doca, thyroid	Died (suddenly) 1 mo. after operation	Not done

from a perineal abscess with septicemia; he died within ten days of the onset of symptoms.

Among the cases reported in the literature, two persons (Cases 6 and 10, Table 1) are still alive.[23,27] Each is presumed to have an infarction of the anterior pituitary. Both suffered postpartum hemorrhage. Each quickly developed many signs of pituitary insufficiency including weakness, lassitude, anorexia, vomiting, hypotension, loss of hair, loss of libido, atrophy of clitoris and labia, amenorrhea, atrophy of breasts, thickened skin, intolerance to cold and mental slowness. These individuals have survived nine and seven years, respectively, with hormonal replacement therapy which has included percortin, thyroid, stilbestrol and, more recently, cortisone. The only surviving patient among our three cases has clear-cut signs of thyroid, adrenal and gonadal hormone deficiencies. He has generalized sarcoidosis and is presumed to have involvement of the anterior pituitary by this process, a not unknown occurrence.[31] He has survived now for three years without replacement therapy.

In five of the previously reported cases and in the three cases reported here the administration of insulin was discontinued within ten days of onset of symptoms. In three other cases previously reported the dosage of insulin was greatly reduced. One patient (Case 5, Table 1) never required insulin and Balo's cases (Cases 1 and 2, Table 1) occurred before insulin was available.

Despite the fall in requirement for insulin some abnormality in the metabolism of carbohydrate persists. In only two of the individuals who no longer required insulin were glucose tolerance tests performed. The curves remained diabetic in type. The intravenous glucose tolerance test in our patient with sarcoid remained diabetic in type. The flat curve after sugar was administered orally indicates to us delayed intestinal absorption.

There are two reports in the literature of surgical removal of the anterior pituitary gland to ameliorate the complications of diabetes mellitus.[29,30] Only two of five individuals have survived the operation. In both of these individuals insulin requirement was somewhat reduced. One individual died four months after the operation, in hypoglycemia. He had pulmonary tuberculosis in addition to diabetes. At autopsy he had slight adrenal-cortical atrophy but no tuberculous involvement of the adrenal glands. The other patient is alive two years after operation. His insulin requirement is 12 units of protamine insulin daily instead of 80 units of protamine insulin. His diabetic state is reported as less erratic and more stable. He requires replacement therapy consisting of cortisone, desoxycorticosterone acetate, desiccated thyroid and testosterone.

SUMMARY

The Houssay phenomenon, so clearly described in experimental animals, has been seen but rarely in man. A study of this phenomenon in man has been made from the review and follow-up of the eleven cases previously reported in the literature and from recent observations upon three individuals who exhibited this phenomenon. This condition, when it occurs, usually involves individuals who have had diabetes mellitus for a considerable time. It is caused usually by infarction of the anterior lobe of the pituitary gland. One of the first effects of the anterior pituitary insufficiency is hypoglycemia. It follows within twenty-four hours after the infarction occurs. In these individuals the hypoglycemia is manifested by bizarre and rapidly changing neurologic signs associated with unconsciousness. These individuals exhibit extreme sensitivity to administered insulin. Those surviving the acute phases of this illness began within a month or two to exhibit the clinical manifestations of deficiencies of thyroid, adrenal and gonadal hormones. Diabetes in these individuals is by no means cured but only ameliorated for the diabetic tendency remains, although the symptoms of diabetes disappear, glycosuria decreases and the level of sugar in the blood approaches the normal level. The response to the stress of intravenously administered glucose is still diabetic in type. Continued administration of insulin to these individuals is sometimes required but the "Houssay man" is quite as sensitive to insulin as the "Houssay dog," and hypoglycemia is always a threat to life.

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Biochemical Alterations during Steroid Hormone Therapy of Advanced Breast Cancer*

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STEROID hormones and castration are successfully employed in the palliative management of advanced carcinoma of the breast.[1–4] Objective improvement occurs in that primary and metastatic lesions decrease in size or disappear, and distressing subjective symptoms diminish in intensity.

In conjunction with an investigation of the clinical and pathologic alterations in advanced breast carcinoma associated with steroid hormone therapy, the accompanying metabolic and biochemical changes were investigated. It was apparent that such studies would aid in the interpretation of the mechanisms of action of the agents employed, as well as serve as a guide to therapy. This report comprises a record and interpretation of the biochemical alterations observed during hormone therapy of advanced breast cancer, and an evaluation of their use in the management of these patients.

Of the patients investigated, a small number were studied intensively on a metabolic ward;[5–8] the majority were studied in the Tumor Clinic. Large doses of androgenic or estrogenic hormones were administered following preliminary observations. No vitamins, iron or other treatment was given, nor were more definitive methods of therapy, such as irradiation, employed during the period of study. Blood chemical determinations were performed at intervals of three days to four weeks, the analytic methods being those employed in the chemical laboratories of the Massachusetts General Hospital.[9]

CALCIUM

Initial Serum Calcium. Initial or pretreatment serum calcium determinations were obtained in 111 patients. Hypercalcemia was considered to be present when the serum calcium exceeded 11.0 mg. per cent, as was the case in eight patients (7.2 per cent). (Table 1.) Of the 111 patients, osseous metastases were demonstrated in fifty patients, of whom six (12 per cent) had hypercalcemia. In two patients with elevated serum calcium, osseous metastases were not detected on roentgen examination. In one of these patients the serum calcium initially was 15.9 mg. per cent and skeletal pain was present; the serum calcium decreased and the pain disappeared on institution of androgenic hormone therapy. Both patients died soon after the onset of hormone therapy from progression of the disease. Postmortem examination revealed extensive osseous metastases in both instances. In no patient with hypercalcemia was there elevation of the serum protein. Marked hypocalcemia was not encountered in this study.

TABLE 1
INITIAL (PRETREATMENT) SERUM CALCIUM VALUES*

Serum Calcium (mg. %)	Osseous Lesions	Soft Tissue Lesions Only	Total Patients
Below 8.0	0	1	1
8.0–9.0	8	9	17
9.0–10.5	35	49	84
10.5–11.0	1	0	1
Over 11.0	6	2	8
Total	50	61	111

* Normal serum calcium: 8.5 to 10.5 mg. per cent. An initial "spontaneous" hypercalcemia was present in 12.0 per cent of the patients with known osseous metastases.

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Serum Calcium during Hormone Therapy. Alterations of the serum calcium were observed in ninety-three patients over a period of several months during estrogenic or androgenic hormone therapy. (Table II.) A decrease of more than 1.0 mg. per cent in the serum calcium was noted in fifteen patients with and without demonstrable osseous metastases. No significant hypocalcemia was encountered. All the patients who exhibited pretreatment hypercalcemia demonstrated a marked decrease of serum calcium to normal levels. There was no accentuation of existing hypercalcemia.

TABLE II
SERUM CALCIUM ALTERATIONS OF MORE THAN 1.0 MG. PER CENT DURING STERO.D HORMONE THERAPY

Hormone Employed	Serum Calcium	Osseous Lesions (x-ray)	Soft Tissue Lesions Only	Total Patients
Androgen	Decreased	4	2	6
	No change	16	7	23
	Increased	6	1	7
Estrogen	Decreased	2	7	9
	No change	13	32	45
	Increased	2	1*	3
Total	Decreased	6	9	15
	No change	29	39	68
	Increased	8	2	10
			Total	93

* Remained within normal range.

Ten of the ninety-three patients had an increase of serum calcium of more than 1.0 mg. per cent during hormone therapy. Eight of these had demonstrable osseous metastases. Seven patients developed serum calcium levels over 11.0 mg. per cent and demonstrated the characteristic syndrome of "induced hypercalcemia."[6] Clinically this consisted of apathy, anorexia, nausea, vomiting and drowsiness. Weight loss, dehydration, disorientation, stupor. coma, vascular collapse and death may occur with severe hypercalcemia. Laboratory studies of the "induced hypercalcemia" state revealed an increase in serum and urinary calcium and a negative calcium balance. No elevation of serum protein accompanied this change.

There was no significant alteration of serum calcium in sixty-eight patients during hormone therapy.

PHOSPHORUS

Initial Serum Phosphorus. The serum phosphorus was recorded in 113 patients before hormone therapy was instituted. (Table III.) Only fourteen had a phosphorus level over 4.5 mg. per cent. Two of these patients had an associated hypercalcemia. However, the two patients with values over 6.0 mg. per cent had normal serum calcium levels though osseous metastases were present. In patients with an elevated serum phosphorus, the serum nonprotein nitrogen was normal. Hypophospha-

TABLE III
INITIAL SERUM PHOSPHORUS VALUES (PRETREATMENT)*

Serum Phosphorus (mg. %)	Osseous Lesions	Soft Tissue Lesions Only	Total Patients
Below 3.0	7	16	23
3.0–4.5	35	41	76
4.5–6.0	8	4	12
Over 6.0	2	0	2
Total	52	61	113

* Normal serum phosphorus, 3.0 to 4.5 mg. per cent. The two patients with values over 6.0 mg. per cent had normal serum calcium and NPN results. The highest value was 6.8 mg. per cent, the lowest 2.2 mg. per cent.

TABLE IV
PHOSPHORUS ALTERATIONS OF MORE THAN 1.0 MG. PER CENT DURING STEROID HORMONE THERAPY*

Hormone Employed	Serum Phosphorus	Osseous Lesions	Soft Tissue Lesions	Total Patients
Androgen	Decreased	15	2	17
	No change	5	2	7
	Increased	3	0	3
Estrogen	Decreased	10	27	37
	No change	7	15	22
	Increased	0	0	0
Total	Decreased	25	29	54
	No change	12	17	29
	Increased	3	0	3
			Total	86

* A decrease occurred in 62.8 per cent.

temia of less than 3.0 mg. per cent was noted in twenty-three patients, the lowest level being 2.2 mg. per cent.

Serum Phosphorus during Hormone Therapy. An initial increase in the serum phosphorus of more than 1.0 mg. per cent occurred in three of eighty-six patients during steroid hormone therapy. (Table IV.) These patients were receiving testosterone. There was no evidence of renal disease or hypercalcemia, although each of the patients in question had osseous metastases. No increase in serum phosphorus was noted during the early period of estrogenic therapy.

A decrease in serum phosphorus of more than 1.0 mg. per cent occurred in fifty-four (62.8 per cent) patients during the administration of hormones. (Table IV.) Of these patients, twenty-seven receiving estrogenic hormone and two receiving androgenic hormone had no demonstrable osseous metastases. In one patient exhibiting the "induced hypercalcemic syndrome" there was an increase in urinary phosphorus, decrease of serum phosphorus and an increase in serum and urinary calcium.

ALKALINE PHOSPHATASE

Initial Serum Alkaline Phosphatase. Serum alkaline phosphatase determinations were carried out in 110 patients before hormone therapy was instituted. Of the forty-seven patients in whom osseous metastases were known to be present, twenty-eight (59.6 per cent) had alkaline phosphatase values over 4.5 Bodansky units (B.U.), and nineteen (40.4 per cent) had values over 6.0 B.U. One patient in the latter group had extensive liver metastases which probably accounted for the elevated phosphatase. (Table V.)

There were sixty-three patients in whom no osseous metastases could be detected on roentgen examination and who had no clinical manifestations of bone involvement. The alkaline phosphatase was elevated above 4.5 B.U. in thirty-seven (57.4 per cent) of these patients, and twenty-two (34.9 per cent) had values over 6.0 B.U. Of this latter group, six patients manifested osseous metastases by x-ray or clinical signs within a few weeks, five had enlarged livers due to metastases, and two later manifested hepatic metastases by enlargement of the liver. Two patients with primary tumors of the breast had extensive Paget's disease of the bone associated with unusual high alkaline phosphatase values. In the remaining seven patients no explanation for the elevated alkaline phosphatase was found.

Serum Alkaline Phosphatase during Hormone Therapy. The alkaline phosphatase was determined serially in ninety-eight patients during hormone therapy. (Table VI.) A decrease in phosphatase level of more than 2 B.U. occurred in twelve patients. There was no apparent correlation with the presence or absence of osseous metastases or the hormones employed. One twenty-seven year old woman with liver metastases, however, demonstrated a decrease in size of an enlarged liver and a decrease in serum alkaline phosphatase during androgen therapy.

An increase in serum alkaline phosphatase of more than 2 B.U. during hormone therapy occurred in twenty-four (53.3 per cent) of the forty-five patients with demonstrable osseous metastases. In only one of these was this due to the presence of obvious hepatic metastases. The increase in alkaline phosphatase activity usually occurred during the first three months of therapy, and after four months tended to decrease, sometimes to pretreatment levels. In one such patient the unusually high value of 71.2 B.U. was recorded shortly after the onset of therapy. The increase in serum alkaline phosphatase was associated with evidence of apparent healing of the osseous lesions, consisting of calcification of previously osteolytic lesions or a more normal appearing osseous structure. Excluding patients with hepatic involvement, of those patients with osseous metastases who had

TABLE V
INITIAL (PRETREATMENT) ALKALINE PHOSPHATASE VALUES*

Alkaline Phosphatase (B.U.)	Osseous Metastases	Soft Tissue Metastases	Total Patients
Normal	19	26	45
4.5–6.0	9	15	24
Over 6.0	19†	22‡	41
Total	47	63	110

* Normal serum alkaline phosphatase 2.0–4.5 Bodansky units per cent.

† One of these had associated liver metastases which partially accounted for the increase.

‡ Of these, six patients manifested osseous metastases within a few weeks, five had enlarged livers due to metastases, two later manifested hepatic metastases, and two had extensive Paget's disease of the bones.

an elevation in serum alkaline phosphatase, 65 per cent (fifteen patients) demonstrated evidence of bone repair. (Table VII.) This is 33 per cent of the forty-five patients treated, a slightly higher incidence of bone repair than the 23 per cent recorded in a larger series.[2]

TABLE VI

ALTERATIONS OF MORE THAN 2 B.U. IN SERUM ALKALINE PHOSPHATASE DURING STEROID HORMONE THERAPY

Hormone Employed	Alteration of Alkaline Phosphatase Greater than ±2 B.U.	Osseous Metastases	Soft Tissue Metastases	Total Patients
Androgen	Decreased	3*	1	4
	No change	7	6	13
	Increased	14†	1†	15
Estrogen	Decreased	3	5	8
	No change	8	31	39
	Increased	10	9‡	19
Total of both hormones	Decreased	6	6	12
	No change	15	37	52
	Increased	24	10	34
	Total	45	53	98

* One patient of this group had liver metastases that decreased in size during testosterone therapy.

† One patient in each of these groups developed liver metastases during hormone therapy that continued to increase in size.

‡ In five patients liver metastases continued to increase in size during therapy to account for this increase, and in 4 patients osseous metastases became manifest during hormone therapy.

An elevation of the serum alkaline phosphatase during hormone therapy occurred in ten of fifty-three patients in whom no osseous metastases were demonstrated. Of these patients, six had progressive enlargement of the liver due to metastases. In the remaining four patients osseous metastases of an osteoblastic type were recognized by x-ray during the course of hormone therapy. Presumably osseous metastases were present in these four patients prior to the institution of hormone therapy. As the result of regression of the tumor and recalcification of the area, dense areas became visible in x-ray films.

ACID PHOSPHATASE

Elevation of the serum acid phosphatase in metastatic carcinoma of the prostate has been shown to be of diagnostic and clinical value. With tumors other than prostatic carcinoma, an increase of serum acid phosphatase activity is occasionally encountered, most frequently in carcinoma of the female breast with osseous metastases.[10] Such an increase was noted in the present study in patients with osseous metastases.

TABLE VII

CORRELATION OF THE INCREASE IN SERUM ALKALINE PHOSPHATASE WITH RESPONSE OF OSSEOUS LESIONS DURING HORMONE THERAPY OF ADVANCED BREAST CANCER WITH OSSEOUS METASTASES

Hormone Employed	Progression of Disease	No Change in Disease	Improvement	
			Moderate	Excellent
Testosterone (13 patients)	4	....	4	5
	30.7%	....	30.7%	38.4%
			69.1%	
Estrogen (10 patients)	3	1	2	4
	30%	10%	20%	40%
			60%	

Acid phosphatase values were determined in the sera of forty-three women with carcinoma of the breast, twenty-seven of whom showed osseous metastases by x-ray examination. Twenty of this latter group had acid phosphatase values over 3.0 Gutman units per cent, while those without osseous lesions showed normal values. The sera of thirty other women gave values below 3.0 units per cent, except those with parathyroid adenomas or Paget's disease.

Two patients demonstrated an unusual alteration of serum acid phosphatase during the administration of testosterone propionate. Patient J. W. was a sixty-five year old woman with extensive osseous metastases studied on the metabolic ward. Initial studies revealed: serum calcium 8.9 mg. per cent, phosphorous 3.9 mg. per cent, alkaline phosphatase 10.2 Bodansky units and acid phosphatase 7.8 Gutman units per cent (normal values 1 to 3 units per cent). Testosterone propionate, 100 mg. intramuscularly, was administered three times a week. At the end of one month the serum alkaline phosphatase was 5.8 B.U. and the acid phosphatase 13.0 Gutman units. At the end of the second month the serum alkaline phosphatase was

5.9 B.U. and the acid phosphatase 9.3 Gutman units. Throughout this period there was continued progression of the tumor as manifested by increased bone destruction. There was no alteration of the serum calcium or phosphorus. Near the end of the third month of therapy an "induced" hypercalcemia developed. The serum calcium was 16.0 mg. per cent, serum phosphorus 3.2 mg. per cent, alkaline phosphatase 8.9 B.U. and acid phosphatase 5.7 Gutman units per cent. A second patient had an increase from 5.0 units of acid phosphatase activity to 7.6 units during testosterone therapy. This also was associated with progression of the disease and an accompanying "induced" hypercalcemia of 13.0 mg. per cent.

NON-PROTEIN NITROGEN

The serum non-protein nitrogen (NPN) was employed as a gross measure of renal function. Of seventy-two patients studied, the NPN was elevated initially in only two patients (2.7 per cent). In one of these the elevation of 48 mg. per cent was due to dehydration, and became normal following hydration. In the other patient with a value of 54 mg. per cent there was an associated spontaneous hypercalcemia. Following initiation of testosterone propionate therapy in this case the serum calcium and serum NPN became normal.

During hormone therapy an elevation of the NPN was noted in two circumstances: (1) the occurrence of hypercalcemia was accompanied by dehydration and a rise in serum NPN. In some of these patients the hypercalcemia and resultant hypercalciuria caused a deposition of calcium in tissues and renal tubules. In one patient this was followed by permanent renal damage. (2) One patient with extensive abdominal metastases demonstrated a rapid increase of the NPN because of obstruction of both ureters by carcinoma.

LIVER FUNCTION TESTS

A limited number of liver function tests were performed prior to and during the period of hormone therapy. The purpose of these tests was to observe changes that might occur with the unusually high doses of estrogenic and androgenic hormones employed, and to determine whether any of the tests would be of value in guiding hormone therapy. It was not the intent to use these determinations as diagnostic procedures for establishing the presence of liver metastases. Since the patients studied had widespread metastatic carcinoma, it is to be presumed that many had hepatic metastases which may have been minimal in extent. Evaluation of the changes of such lesions during hormone therapy would be difficult. For investigational purposes only those patients with obvious hepatic metastases were studied with respect to liver function changes during hormone therapy.

The liver function tests most frequently employed were the estimation of serum proteins, the cephalin flocculation test and the serum alkaline phosphatase. The van den Bergh test was not routinely employed because it appeared to be a gross test of liver function in patients with metastases to the liver and, if elevated, was associated with the obvious presence of hepatic metastases. Dye excretion tests, such as the bromsulfalein test, were not employed since even in the presence of hepatomegaly due to neoplastic disease they do not distinguish between the presence and absence of liver metastases.[11]

Serum Proteins. Of seventy-eight patients, the initial (pretreatment) serum total protein was normal in sixty-nine or 88.4 per cent of the patients. Values below 6.0 gm. were recorded in five patients. Four of these had ascites or pleural effusion, and one had extensive carcinomatous disease. The lowest value was 5.0 gm. per cent. An elevation of the serum protein was noted in four patients, including one with extensive hepatic metastases. The highest value was 8.6 gm. per cent. None of the patients with an elevated serum protein had an associated hypercalcemia.

During hormone therapy no increase in the serum total protein was observed. No patient in whom the "induced hypercalcemic syndrome" developed had an associated increase of the serum total protein. Only two patients demonstrated a significant decrease in total protein; the lowest value being 4.3 gm. per cent. Both patients had rapid progression of the disease during this period. Patients in a terminal state and not receiving hormonal therapy were not studied.

Cephalin Flocculation Test. In forty-four patients the forty-eight-hour cephalin flocculation test was carried out before hormone therapy was initiated. This test was normal in forty-one patients, although three of these had enlarged livers due to metastases. The cephalin floccula-

tion was 3-plus in three patients, two of whom had a palpable liver due to metastases. The other patient had no other evidence of hepatic disease during the ensuing two years.

The three patients with liver metastases demonstrating a normal cephalin flocculation test, and four others in whom liver metastases developed during hormone therapy, had no increase in flocculation in subsequent cephalin flocculation tests. Patients without liver metastases showed no alteration in the test during hormone therapy.

Van den Bergh Test. In fifteen patients serial serum bilirubin determinations were made. Only one was elevated initially, and this patient had a palpable liver and was clinically jaundiced within a week. Three patients with enlarged livers due to metastases initially had normal van den Bergh tests. Despite hormone therapy the disease progressed and the serum bilirubin became elevated. In eleven patients who did not have apparent liver metastases, there was no alteration of the van den Bergh test during hormonal therapy.

An increase in serum bilirubin occurred in association with hypercalcemia in three patients.[6] Values of 1.8, 2.5 and 2.8 were recorded at the peak of the "induced hypercalcemic syndrome." There was no evidence of hepatic failure.

Alkaline Phosphatase. The alteration of serum alkaline phosphatase that occurrs in association with osseous metastases and during hormonal therapy has already been described. The serum alkaline phosphatase is also an index of liver function in the absence of osseous lesions, and on occasion may be of value despite the presence of osseous metastases.

The serum alkaline phosphatase was elevated initially in five patients with extensive metastases without demonstrable osseous lesions. In only one of these (J. M.) were the cephalin flocculation and van den Bergh tests both abnormal. In all five patients an increase of alkaline phosphatase occurred during hormonal therapy as the disease steadily progressed. (Table VIII.)

In two patients with associated osseous lesions there was excellent objective improvement of the disease during hormone therapy in that the liver decreased in size and osseous lesions were more normal on x-ray examination. In one of these (E. K.) the initial alkaline phosphatase was normal, and the slight rise noted during hormone therapy was regarded as due to the increased osteoblastic activity of bone repair. The other patient (Y. L.) with an initial value of 9.2 B.U. had a decrease in alkaline phosphatase to 5.7 B.U. during hormone therapy. This was postulated as due to a decrease in liver damage, but with a value above normal as a result of osteoblastic activity of bone repair.

TABLE VIII
SERUM ALKALINE PHOSPHATASE (B.U.) IN PATIENTS WITH KNOWN LIVER METASTASES PRIOR TO AND DURING HORMONE THERAPY

Patient	Age (yr.)	Osseous Metastases	Pre-treatment	During Treatment
E. K.	29	+	3.4	6.7
Y. L.	27	+	9.2	5.7
H. L.	56	0	6.3	39.6
J. M.	61	0	24.6	42.6
A. P.	53	0	15.8	26.5
M. S.	42	0	21.3	47.0
A. S.	33	0	36.4	48.6

HEMATOPOIETIC SYSTEM

The administration of androgenic and estrogenic hormones to patients with advanced breast cancer produced alterations in the hematopoietic system. Of note were those changes observed in the hemoglobin, red blood cell count and hematocrit. (Table IX.) The alterations of the latter two mirrored those of the hemoglobin.

TABLE IX
ALTERATION OF HEMOGLOBIN DURING HORMONE THERAPY OF ADVANCED BREAST CANCER

Hormone Employed	De-crease >2 gm.	No Change ±2 gm.	In-crease >2 gm.	Total Patients
Estrogen				
Number of patients	6	32	4	42
Per cent	14.2	76.2	9.5	..
Androgen				
Number of patients	0	17	16	33
Per cent	....	51.5	48.5	..

Repeated blood examinations of forty-two patients receiving estrogenic hormones showed that in 76.2 per cent (thirty-two patients) the hemoglobin varied less than plus or minus 2 gm.

Six patients (14.2 per cent) had a decrease of more than 2 gm. during therapy and this was associated with progression of the disease. Four patients (9.5 per cent) had an increase of more than 2 gm. in the hemoglobin. Three of these patients had extensive osseous metastases. All four patients had striking clinical improvement as a result of hormone therapy. The highest values recorded were a hemoglobin of 15.4 gm. and 6.8 million red blood cells. In one patient with osseous metastases which improved, the hemoglobin rose from 6.4 to 12.0 gm. In the patients with an increase in hemoglobin and red blood cell count, the bone marrow activity was within normal limits.

Androgenic hormone therapy was associated with an unusual alteration in erythropoietic activity. Of thirty-three patients receiving androgen therapy, seventeen (51.5 per cent) had a decrease of the hemoglobin of not more than 1.0 gm. or an increase of less than 2.0 gm. No patient had a decrease of more than 1.0 gm. despite progression of the tumor. Sixteen patients (48.5 per cent) had an increase of hemoglobin of more than 2.0 gm. This increase was not necessarily accompanied by improvement of the disease nor could it be correlated with the presence or absence of osseous metastases. There was an apparent dissociation between the clinical course of the tumor and the increase in red blood cell activity which appeared. The highest value recorded was a hemoglobin of 18.0 gm., 6.5 million red blood cells and a hematocrit of 59 per cent. The greatest increase in any one patient was from 11.3 to 18.0 gm. of hemoglobin. These changes appeared to be a result of hormone therapy. No transfusions, iron or supplemental vitamins were administered. Bone marrow aspirations revealed hyperplasia of the erythrocyte series.

The increase in erythrocyte activity on administration of large doses of androgen therapy was accompanied by unusual clinical signs.[12,13] The complexion, especially the skin of the face and anterior neck, of patients treated over a long period became ruddy and flushed. Injection of the conjuctiva was present. Although the flushing and ruddiness would disappear in a few days after discontinuing androgen therapy, the hemoglobin remained elevated for longer periods of time. The high values, however, were not maintained indefinitely.

In one patient who received ethinyl estradiol and then testosterone propionate there was an increase in the hemoglobin from 6.4 to 18.0 gm., and an increase of red blood cells from 2.4 to 5.9 million per cu. mm. This was accompanied by improvement of the osseous lesions.

COMMENTS

Significant biochemical and metabolic changes have been observed during administration of sex steroid hormones in patients with metastatic carcinoma of the breast. The alterations noted further clarify the mechanisms of tumor regression occurring during hormone therapy, and allow selection of specific biochemical determinations as therapeutic guides in the management of such therapy.

Pathologic examination of tumor masses undergoing regression during hormone therapy revealed the immediate cause of softening of the tumors to be a loosening of the connective tissue surrounding tumor cells. Collagenous stromal bands were reduced to narrow tangled fibrous strands separated by wide interspaces. The widened interspaces contained altered cancer cells, infiltrating plasma cells and lymphocytes, and a tangle of delicate fibrils. Concurrently with this loosening of stroma, tumor cells degenerated and disappeared. The process of loosening reversed and fibrosis of the area occurred with accumulation of mature collagen. During this later process elastic tissue fibers were deposited over large areas. Osseous lesions undergoing regression further demonstrate the formation of new bone. The histologically more differentiated tumors and the clinically more slowly growing tumors appeared more responsive to hormone therapy.[14,15]

X-ray examinations of osseous metastases initially revealed osteolytic lesions in most instances. In patients with a clinically slower progressing tumor a small rim of increased density is noted about the osteolytic (osteoclastic) lesions and appears to represent an attempt at bone repair (osteoblastic activity). Occasionally, the lesions are largely of increased density and are referred to as osteoblastic metastases. These appear to be slower growing lesions, sufficient time elapsing to allow an intense reparative reaction to occur about and within the metastasis. In patients in whom there is no improvement during hormone therapy the osteolytic lesions continue to increase in size and extent. In those patients demonstrating improvement as a result of therapy, the metastatic lesions become dense (osteoblastic repair with calcifica-

tion) or the bones appear to be normal in structure. Relative differences in the degree of repair are noted in patients with less striking improvement; in many, both continued progress of osteolytic metastases and the formation of osteoblastic (repaired) lesions are present.

Such reparative or progressive processes noted on x-ray and pathologic examination were correlated with the biochemical determinations observed.

Calcium. It is recognized that the processes of bone formation (osteoblastic activity) and bone reabsorption (osteoclastic activity) occur simultaneously in the normal individual. The presence of osseous metastases disrupts this normal pattern in the areas of the tumor, and this disruption is in part manifested by alterations of calcium metabolism. Varying degrees of elevation of the serum and urinary calcium have been observed to occur in patients with cancer in association with osseous metastases. Such increases are found particularly in patients with breast cancer, in which the lesions are predominantly osteolytic.[17] In patients with extensive metastases or a rapidly growing tumor the bone destruction is so great as to result in excessive release of calcium from the bone and marked increase in serum calcium levels occur. The "spontaneous hypercalcemia syndrome" is invariably accompanied by characteristic signs and symptoms. Intermediate variations in the clinical and chemical findings are more common, and the symptoms and signs are usually subtle or absent. The diagnosis in such instances is as a rule made only by laboratory studies. In patients in whom this syndrome is severe or longstanding, calcium deposition may occur in various tissues and in the renal tubules, resulting in uremia and at times irreversible renal damage. It was in this respect that non-protein nitrogen determinations were of value in observing the patient's course.

In the present study untreated patients with osteolytic metastases had a normal or elevated serum calcium. Low values were not encountered. Spontaneous hypercalcemia occurred in 12 per cent of patients demonstrating osseous metastases by x-ray examination. In two patients hypercalcemia preceded the detection of osseous lesions by x-ray examination. It would appear that hypercalcemia in the untreated patient with advanced cancer of the breast is indicative of osseous metastases although not demonstrable on roentgenologic examination, and that the presence of active breast cancer without osseous involvement has no direct effect on the calcium metabolism.

In no patient with hypercalcemia was there elevation of the serum protein; hence, the increase in serum calcium apparently was not due to an increase in the protein-bound fraction.

The presence of breast cancer elicits a primary attempt at repair by the host,[14,15] and bone at the site of metastases may exhibit increased osteoblastic activity. However, if the rate of cancer growth and bone destruction is rapid, osteolysis may be sufficient to cause hypercalcemia.

Observation of the serum calcium during steroid hormone therapy aided in evaluating the effect of such therapy on the tumor. In patients with initial "spontaneous" hypercalcemia the serum calcium decreased to normal values. It is presumed that excessive osteolysis of bone due to tumor was inhibited. The regression of tumor growth apparently resulted in decreased bone breakdown, increased osteoblastic activity, new bone formation, increased calcium deposition, and hence a decrease in serum calcium and urinary calcium excretion. The presence of hypercalcemia is not a contraindication to the institution of steroid hormone therapy. In some instances the decrease of serum calcium may be a direct effect of the hormone on calcium metabolism, as recorded in other bone disease. No hypocalcemia was detected.

A condition referred to as the "induced hypercalcemia syndrome" occurred in a limited number of patients.[5] This syndrome, manifested by drowsiness, anorexia, nausea, vomiting, dehydration, stupor and coma, may terminate fatally. Close observation of the patient receiving hormone therapy is necessary so that corrective therapy can be instituted early. In our experience no patients clinically free of skeletal metastases have developed hypercalcemia during hormonal therapy. Estrogenic hormones seldom produced hypercalcemia in patients with osseous metastatic lesions whereas the occurrence of this syndrome during androgenic therapy, although infrequent, was more common. With the use of either hormone the development of the symptoms described in patients with demonstrable osseous metastases from breast cancer should be considered as presumptive evidence of impending hypercalcemia, even though the laboratory findings are within normal limits.

A clear explanation of this phenomenon is not

available. Investigations suggest several possibilities: (1) an initial acceleration of tumor growth with rapid bone destruction resulting in hypercalcemia and hypercalciuria, (2) interference by the hormones of the spontaneous attempt at bone repair, or breakdown of tumor barriers, (3) a direct effect of the hormones on calcium metabolism, (4) a similarity in the alterations to that of parathyroid hormone with an increase of urinary phosphorus, hypophosphatemia, hypercalcemia and hypercalcuria,[4,5] and (5) immobilization.

Phosphorus. The estimation of serum phosphorus was important initially only in reference to later hormone therapy and evaluation of progress of the disease, rather than as a diagnostic aid. The serum phosphorus initially was elevated above 6 mg. per cent in only two patients with osseous metastases. Neither had hypercalcemia or renal disease. With excessive bone destruction an increased serum phosphorus might be expected, usually in association with a high serum calcium. Hypophosphatemia was present in twenty-three patients. Secondary parathyroid hyperplasia might conceivably be present in those patients with osseous metastases, but the low levels in patients without demonstrable osseous lesions are not explained. A low serum phosphorus has been detected previously in patients with advanced skeletal metastases or cachexia.[17]

A decrease of serum phosphorus of more than 1.0 mg. per cent occurred in fifty-four patients (62.8 per cent) during hormone therapy. As a rule this decrease was maintained as long as the tumor was controlled or the hormone administered. The fall in serum phosphorus during endocrine therapy might be due to a reduction in the rate of bone destruction. This may be true with testosterone therapy. However, twenty-seven patients receiving estrogenic hormone and in whom no osseous metastases were demonstrated also had a reduction of serum phosphorus; patients without osseous metastases manifested a decrease in serum phosphorus as frequently as those with osseous lesions. The fall in serum phosphorus does not appear to be solely an effect of the treatment on the metastatic tumor, since in patients with postmenopausal osteoporosis the serum phosphorus fell in almost all instances when estrogens were administered.[18] There was no correlation between the fall in serum phosphorus and the initial clinical response of the tumor during hormone therapy. Furthermore, no significant correlation could be made between the decrease in serum phosphorus and the development of fluid retention. In the absence of similar decrease of other chemical components it would appear that this phenomenon is not the result of increased body fluid and resultant hemodilution.

In one metabolic study of a patient with extensive osseous metastases the alterations noted were similar to those that occur with the administration of parathyroid hormone; that is, an initial increase in urinary phosphorus, fall in serum phosphorus, rise in serum calcium and an increase in urinary calcium.[6,8] This patient demonstrated the "induced hypercalcemic syndrome."

It has been reported that during the administration of testosterone or estrogenic hormones to patients with active gigantism and active acromegaly, the elevated serum phosphorus decreased and the phosphorus balance became more positive. It was also noted that in the growing child there is an elevation of serum phosphorus which falls to the adult level shortly after the onset of puberty. It has been proposed that serum phosphorus may be an index of pituitary growth hormone production in human subjects, and that estrogen or testosterone inhibit the production of pituitary growth hormone.[19] Postulation of a similar relation in breast cancer is possible and warrants further intensive investigation.

In some patients whose tumor regressed during hormone therapy a rise in serum phosphorus occurred just prior to and during an exacerbation or progression of the tumor despite continued hormone therapy. It has been possible to predict a forthcoming "escape" of the tumor from hormone therapy and subsequent progression of the disease by this increase in serum phosphorus which may not be accompanied by hypercalcemia.

Alkaline Phosphatase. It is clear that abnormally increased osteoblastic cell activity is accompanied by an elevated alkaline phosphatase of the circulating blood, roughly proportional to the extent and intensity of the attempt at ossification.[16] When destructive (osteolytic) and reparative (osteoblastic) processes occur simultaneously, as in osseous metastases, the constructive process alone is reflected in the alkaline phosphatase activity of the blood serum. In tumors without bone or liver involvement the serum phosphatase activity is usually

normal.[16] The elevation of serum alkaline phosphatase in liver disease is a well defined entity.

The alterations of serum alkaline phosphatase are a manifestation of both hepatic and osseous changes. The distinction between these factors is necessary in interpreting the initial values obtained, as well as in evaluating later changes during hormone therapy. The alkaline phosphatase is elevated during the processes of new bone formation or increased osteoblastic activity. This activity is stimulated in part by the ordinary strain or stress of mobilization. In patients with rapid destruction of bone due to breast cancer metastases an unsuccessful attempt at "spontaneous" bone repair may occur. If the disease is slower growing, the normal defense mechanism of the body may attempt bone repair (increased osteoblastic activity) about the site of the invading lesion, resulting in an increased serum alkaline phosphatase and a rim of increased density about the lesion on x-ray examination. A similar change may occur in the presence of a pathologic fracture with repair. Of the patients with osseous metastases, nineteen (40.4 per cent) had serum alkaline phosphatase levels above 6.0 B.U. Only one of these had liver metastases. In those without demonstrable liver metastases, the values did not exceed 15 B.U., nor did they increase as rapidly as in patients with liver metastases. Since breast carcinomas with a lower degree of malignancy appear to respond favorably to hormone therapy, those patients with elevated serum alkaline phosphatase without liver involvement might be expected to do well. Outstanding regression of bone lesions occurred in twelve of the nineteen patients with elevated alkaline phosphatase levels. In two patients with Paget's disease of the bone, the serum alkaline phosphatase was higher (30 and 24 B.U.) than that usually seen in patients with osseous metastases.

In twenty patients without osseous metastases or Paget's disease, the serum alkaline phosphatase was elevated over 6 B.U. Six of these patients manifested osseous metastases within a few weeks. In seven patients the increase in alkaline phosphatase activity was due to liver metastases that were already present or were manifest clinically soon thereafter; the degree of elevation being from 10 to 36 B.U. The alkaline phosphatase appeared to be the most sensitive guide for the detection of hepatic metastases. Elevation of the serum alkaline phosphatase has been described in patients with liver metastases even when there was no elevation of the serum bilirubin.[20–22] It has been found that the extent of elevation and the frequency of these elevated values increase with the extent of the metastatic involvement of the liver.[22,23] Since the tumor cells contain less than normal amounts of alkaline phosphatase, it is unlikely that these cells are the source of the enzyme.[24]

It is apparent that in patients with advanced cancer of the breast an elevation of the serum phosphatase may be indicative of hepatic metastases or osseous metastases even though lesions are not demonstrable on roentgen examination.

During hormone therapy of patients with osseous metastases but without hepatic metastases, an increase of the serum alkaline phosphatase was observed in 51.1 per cent. All the patients with osseous metastases who responded favorably to hormone therapy had an associated rise in the serum alkaline phosphatase. There is no evidence that this was due to direct stimulation of osteoblastic activity. Previous studies in patients with postmenopausal osteoporosis demonstrated no change in the serum alkaline phosphatase during estrogenic or androgenic hormone therapy.[25] This suggests that as a result of the decrease in size of the tumor attempts at bone repair (osteoblastic activity) has occurred. Furthermore, stimulation of normal tissue repair may occur, similar to that noted in the primary breast tumor undergoing regression during hormone therapy.[14,15] In patients with widespread carcinoma of the breast without osseous lesions demonstrable by x-ray, the presence of such metastases may be presumed from the increase in serum alkaline phosphatase during hormone therapy. Relief of pain and appearance of osteoblastic lesions on x-ray are further evidence of the presence of such lesions.

In eleven patients no reason could be assigned for the decrease of alkaline phosphatase that occurred. It may be postulated that the hormone agent employed impaired the normal reparative osteoblastic activity by stimulation of tumor growth.

During hormone therapy progression of hepatic metastases was associated with a steady increase in serum alkaline phosphatase. In a few instances, when regression of the liver metastases occurred, the alkaline phosphatase decreased to normal values. If, however, osseous metastatic

improvement occurred concurrently, the alkaline phosphatase decreased but to a level above normal; the persistence above normal being the result of osteoblastic activity.

An explanation for the elevation of alkaline phosphatase due to liver metastases has been postulated.[23] As the hepatic tumor mass enlarges, it compresses and distorts the surrounding hepatic tissue. The intrahepatic bile ducts near the mass are obstructed, leading to a biliary obstruction similar to that of ligation of minor extrahepatic ducts in animals, and the serum alkaline phosphatase increases. The greater the number of tumor nodules, the greater the number of ducts obstructed; hence the higher the serum alkaline phosphatase. When a sufficient number of ducts are blocked, jaundice occurs. Consequently, when hormonal therapy results in the reduction of tumor size, the biliary ducts are no longer obstructed and the alkaline phosphatase decreases.

In the present investigation, as in previous studies, it would appear that the serum alkaline phosphatase determination was the only liver function test employed that was of significant value in detecting liver metastases even in early stages. The presence of osseous lesions must be considered in evaluating this method of detecting impairment of liver function.

Acid Phosphatase. An increase in serum acid phosphatase was noted in patients with osseous metastases. Two patients demonstrated an increase in the acid phosphatase during hormone therapy, eventually associated with an "induced hypercalcemic syndrome."

Slight increases in serum acid phosphatase in hyperparathyroidism have been observed to fall promptly to normal values following removal of parathyroid adenomas. Since bone contains small amounts of acid phosphatase, it has been suggested that the "bone acid phosphatase" may be the origin of small increases in serum acid phosphatase in hyperparathyroidism.[10] Similarly, it would appear that in patients with osseous metastases from breast cancer the increase in serum acid phosphatase during hormone therapy was due to an increased rate of bone destruction and mobilization of "bone acid phosphatase." The eventual development of hypercalcemia further supports this premise. The hormone administered presumably had no effect on the normal rate of progression of the disease, or stimulated the rate of tumor growth increasing the rate of bone destruction.

Liver Function Tests. Liver function studies were conducted to observe alterations that might occur as a result of intensive hormone therapy. No significant alteration of the serum total protein occurred. The changes noted were those anticipated in patients with extensive debilitating disease. The use of this test as a guide to hormone therapy of breast cancer does not appear to be of value. The cephalin flocculation test, although affected by the presence of liver metastases, did not appear to be of diagnostic aid in ascertaining the presence of metastases until these lesions were easily demonstrable clinically. Despite the presence of extensive liver metastases, the van den Bergh test remained within normal limits, nor did hormonal therapy alter the test. The serum bilirubin became elevated only when extensive liver metastases were easily demonstrable clinically, and was not a useful guide for hormone therapy. The bilirubinemia that occurred during the "induced hypercalcemia syndrome" is of interest and might possibly be explained by red cell hemolysis or to increased viscosity of the blood.[26] The serum alkaline phosphatase, as already indicated, was the only liver function test employed that was of significant value in all stages of liver metastases.

Hematopoietic System Alterations. It was apparent that a decrease of erythroid activity during estrogenic hormone therapy was associated with progression of the cancer. The extensive involvement of bone marrow and/or decrease in the nutritional status of the patient were prominent features. The increase in erythroid activity, conversely, was associated with improvement in nutritional status and/or regression of osseous metastases, resulting in more normal marrow activity.

The dissociation between the clinical course of the tumor and the increased erythroid activity during androgenic hormone therapy suggests that androgenic hormones may be a stimulus to the marrow. That this hormone may play a role in folic acid metabolism has also been suggested.[27]

Biochemical Aids for the Management of Hormone Therapy. By analysis of the biochemical alterations occurring during hormone therapy, a method for management of hormone therapy in patients with advanced breast cancer can be outlined. It would appear that certain chemical determinations are necessary as an aid in establishing the presence and site of metastases

and in evaluating the tumor response to therapy. Initially, the following procedures are carried out: serum calcium and phosphorus, serum alkaline phosphatase, BUN or NPN, and hemoglobin. At the end of one week a serum calcium is obtained for detection of early hypercalcemia. Thereafter, these procedures are repeated at intervals of three to six weeks. After four months further studies are obtained as indicated. In patients receiving long term hormone therapy, or in whom response to therapy has been favorable, determination of the serum calcium, phosphorus, alkaline phosphatase and hemoglobin every two to four months aids in anticipating new changes in tumor growth. In conjunction with these studies, appropriate x-ray examinations are conducted. By such procedures evaluation of the progress of the tumor can be made, and improved patient care thereby attained.

SUMMARY

1. Determinations of serum calcium and alkaline phosphatase are of value in establishing the presence of osseous and hepatic metastases in advanced breast cancer.

2. Steroid hormone therapy for advanced breast carcinoma produces biochemical alterations in the blood which aid in evaluation of the tumor response to such therapy.

3. The serum calcium, phosphorus, nonprotein nitrogen and alkaline phosphatase appear to be important guides in long term hormone therapy of advanced breast cancer.

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The Pathogenesis of Anemia in Patients with Carcinoma*

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RECENT investigation of the development of anemia in association with lymphomas and leukemia has placed emphasis on the role of hemolysis. Ross,[1] Tedeschi,[2] Berlin[3] and others have independently described the frequency of accelerated red cell destruction in such patients. A small percentage of these patients shows overt hemolytic phenomena but in the majority more sensitive methods are required to demonstrate this anomaly.

In a preliminary report from this laboratory[4] use of the Ashby technic for study of the red cell life span demonstrated a considerable acceleration of destruction of the transfused normal cells in a small number of patients with carcinoma. In order to study this problem more fully, attention in the present investigation is directed toward two factors: (1) The role of hemolysis as measured by routine clinicopathologic tests and the Ashby technic, and (2) the rate of erythropoiesis. In the latter study interpretation of the marrow aspirate was combined with evaluation of the ferrokinetics of erythropoiesis, utilizing the radioisotope Fe^{59}.

MATERIALS AND METHODS

Forty-five patients with many types of biopsy-proved carcinoma were chosen. In these patients all studies failed to demonstrate any overt cause for anemia such as blood loss. They were not receiving and had not recently received any therapy which might lead to anemia or might depress marrow function, such as radiotherapy, tumor chemotherapy or transfusion. In every instance either skeletal x-ray survey, marrow aspiration and/or ultimate necropsy showed that the disease was widely disseminated. The types of epithelial neoplasm included carcinoma of the lung, breast, stomach, esophagus, prostate, kidney, ovary and thyroid.

TABLE 1
CLASSIFICATION OF HEMOLYSIS

Procedure	Normal	Slight	Moderate	Marked
Mechanical fragility (%)	<5	5–10	>10	>10
Osmotic fragility	0.45–0.50	>0.50	>0.50	>0.50
Reticulocyte count (%)	<3	3.1–5	5.1–10	>10
Fecal urobilinogen (E.U./100 gm.)	<200	200–350	350–600	>600
Urine urobilinogen	1/10–1/160	1/320–1/640	>1/640	>1/640
Coombs' test (direct)	Negative	Negative	Positive	Positive
Bilirubin-delayed (mg. %)	0.1–1.0	1–2	2–5	>5

Anemia was present in more than 90 per cent of the patients at the outset of the investigation and eventually in all cases.

The clinicopathologic studies are those routinely used (Table 1) and are fully described in a previous report.[4] The Ashby technic employed was that described by Kaplan and Zuelzer.[5] Patients were so selected that the great majority had never had previous transfusions.

Plasma iron and iron-binding capacity were determined by the Kitzes[8] and Cartwright[9] method. The plasma and red cell iron turnover was calculated by the Hennessy-Huff equation.[10] Radioactive iron-59 was obtained from the Atomic Energy Commission as ferric chloride in dilute hydrochloric acid. The amount of

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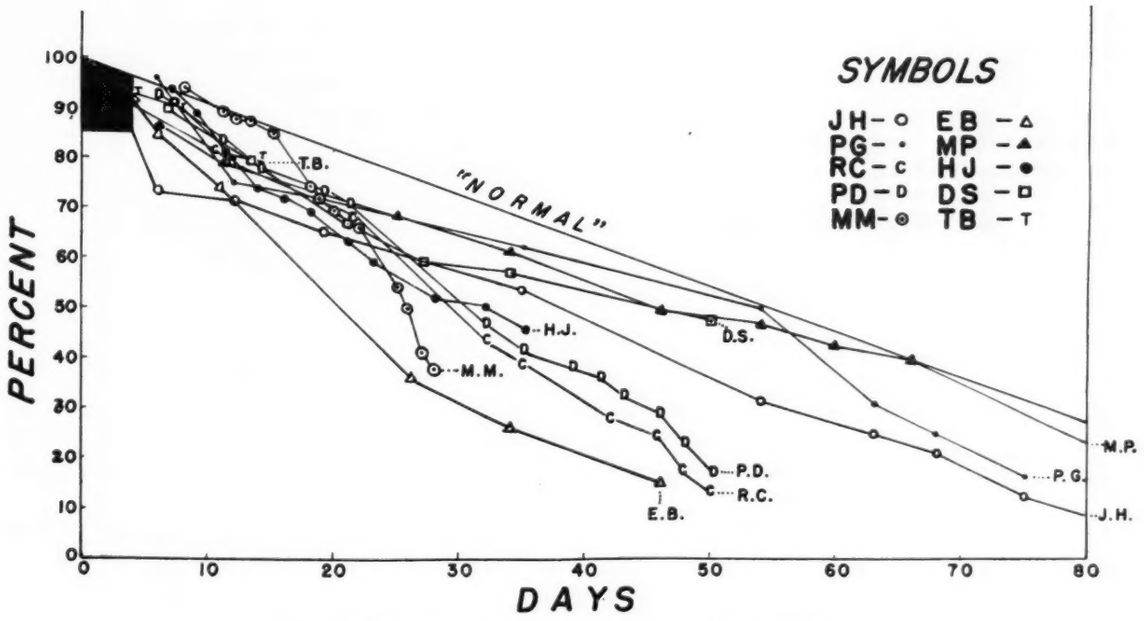


FIG. 1. Ashby-type curves in ten patients with carcinoma.

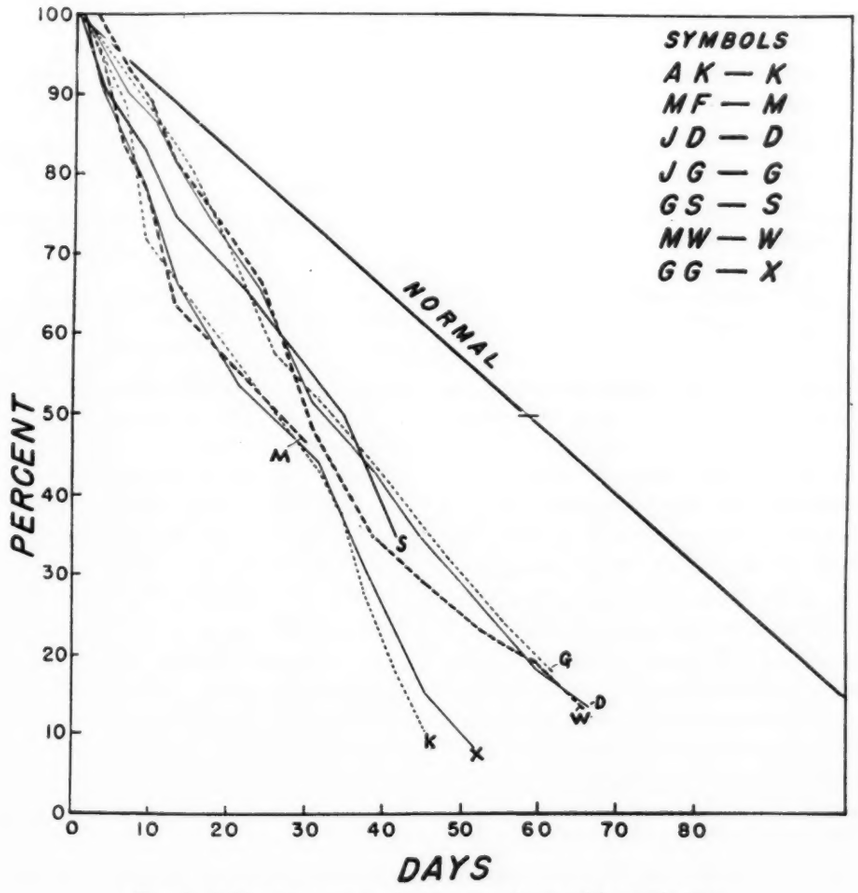


FIG. 2. Ashby-type curves in seven patients with carcinoma.

radioactivity injected was approximately 5–10 microcuries/patient.

RESULTS

Clinicopathologic Observations. Twenty-six patients with carcinoma were studied by the usual multiple clinicopathologic tests. A moderate increase in hemolysis was found in one patient (4 per cent), a slight increase in hemolysis in fourteen (54 per cent) and no significant change in eleven (42 per cent). Further details are given in Table II.

Ashby Data. Ashby-type studies, using the blood of healthy donors were made nineteen times in seventeen patients with a variety of carcinomas, and eleven times in ten patients with neoplasms other than carcinomas including a variety of blood dyscrasias. In the patients with carcinoma (Figs. 1 and 2) fifteen of the nineteen studies showed a moderate to marked increase in the rate of destruction of the transfused cells. In all of these fifteen instances 50 per cent of the transfused cells were destroyed in thirty-five days or less. Three of the patients showed a slight increase in the rate of destruction of the transfused cells and in one patient the Ashby curve was approximately normal. In two instances (Fig. 3) repeat studies revealed further increase in the rate of hemolysis in association with progression of the disease.

For comparison, data on ten patients with neoplastic disease other than carcinoma (such as chronic myeloid leukemia, chronic lymphatic leukemia, agnogenic myeloid metaplasia, multiple myeloma, Hodgkin's disease and fibrosarcoma) were summarized in Figure 4. In all eleven instances in which studies were made

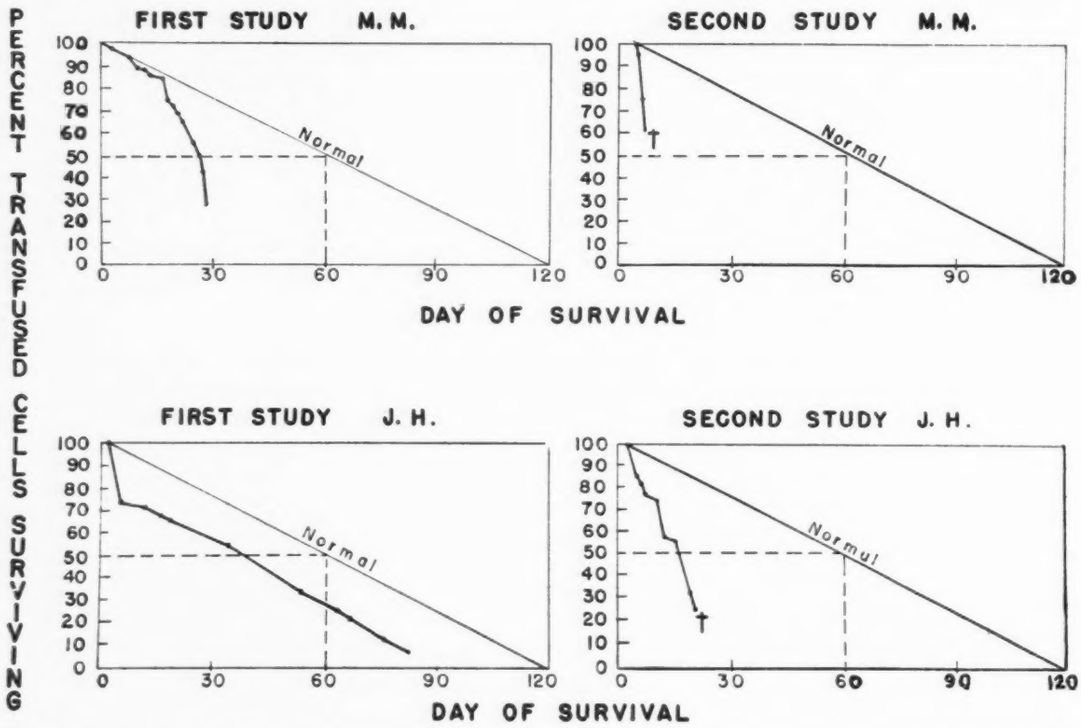


FIG. 3. Characteristic Ashby-type curves in two patients with neoplastic disease and repeat studies when the disease progressed.

TABLE II

DEGREE OF HEMOLYSIS IN TWENTY-SIX PATIENTS WITH CARCINOMA (ROUTINE STUDIES)

Estimated Degree of Hemolysis	Total	Clinicopathologic Findings: Elevation above Normal Values				
		Reticulocytes	Fecal Urobilinogen	Urine Urobilinogen	Indirect Bilirubin	Mechanical Fragility
None	11(42%)	..	..	..	..	..
Slight	14(54%)	12	2	5	..	4
Moderate	1(4%)	1	..	..	..	..
Total	26(100%)	..	..	..	..	..

moderate to marked acceleration of the rate of destruction of donor cells was found. The "shift to the left," or more extreme shortening of the life span, was greater in this group than in the patients with carcinoma.

plasma iron level, as found in thirty-one of our forty-five patients, in association with depression of plasma iron-binding globulin. Therefore the saturation percentage may show normal results, as occurred in fourteen of our forty-five patients.

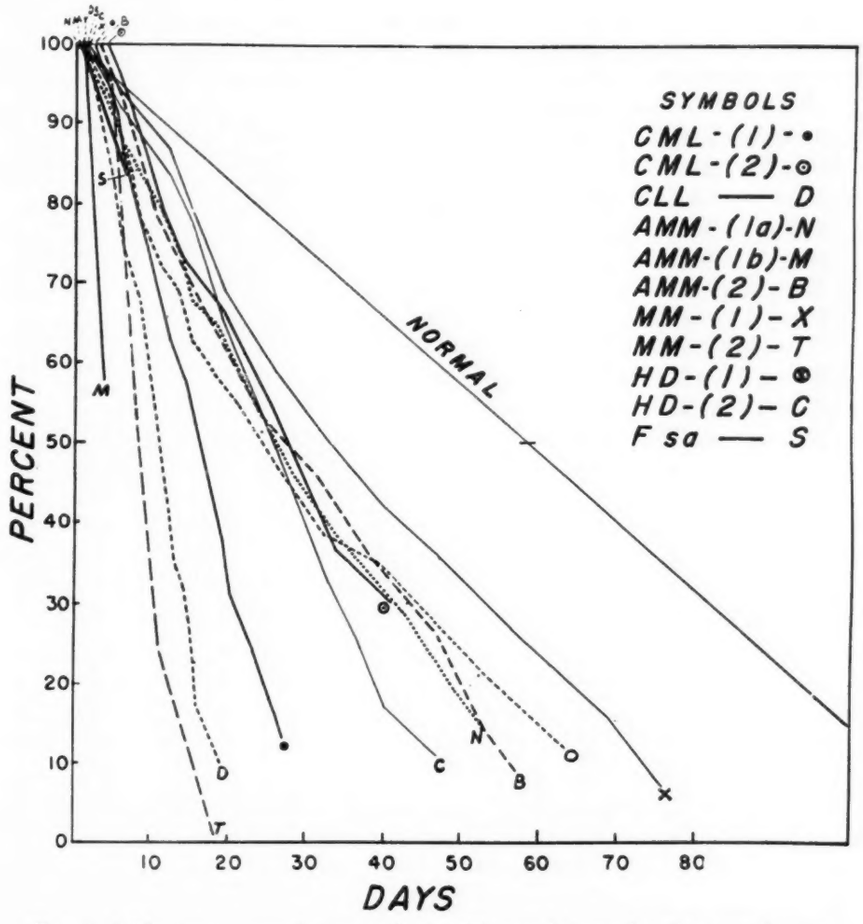


FIG. 4. Ashby-type curves in ten patients with neoplasms other than carcinoma.

Marrow Activity. In forty-five patients bone aspirates gave positive results for tumor cells. When the degree of cellularity or marrow activity was estimated, only four (8 per cent) exhibited decreased cellularity, thirty-five (78 per cent) gave normal or slightly decreased results and six (14 per cent) were found to have increased in the degree of cellularity.

Studies of Iron Metabolism. Forty-five patients with documented carcinoma were studied using Fe^{59} combined with iron-binding globulin (Cohn-fraction IV-7*). In this type of patient the most frequent observation is a depression of

Ferrokinetic studies are summarized in Tables III and IV. As can be seen, the half-time value for the removal of plasma Fe^{59} following intravenous injection, normally reached in sixty to 120 minutes, was shortened in nineteen of the patients and normal in sixteen. In only ten of the forty-five patients, or 22 per cent, was there prolongation of this half-time value. When attention is directed to plasma iron turnover in milligrams per day, it will be noted that many of the patients (twenty-one of forty-five, or 47 per cent) gave normal values. Red cell iron turnover data generally gave either normal or increased results. Both plasma iron removal rates and red cell iron renewal rates frequently increased. Calculation of red cell iron

* This fraction was supplied by Dr. Joyce M. Flynn, University Laboratory of Physical Chemistry, Harvard University, Boston, Mass.

utilization after fourteen days indicated that 69 per cent of the patients had normal values.

COMMENTS

Routine clinicopathologic tests gave little indications of increased hemolysis. The only abnormalities found were: (1) a slight elevation of the reticulocyte level in one-half of these patients; (2) an elevation of fecal urobilinogen in two patients, and (3) a mild increase in the mechanical fragility in urinary urobilinogen in one-fourth of the patients. The vast majority of patients showed either no evidence or very slight evidence of the increased hemolysis revealed by more refined studies.

A Coombs cross matched, Ashby-type transfusion was given in thirty instances in the course of this study. Nineteen of the studies in patients with advanced carcinoma revealed a moderate to marked increase in the rate of destruction of the transfused normal cells. Eleven studies in patients with non-carcinomatous neoplastic

TABLE III

SUMMARY OF DATA ON IRON METABOLISM IN FORTY-FIVE PATIENTS WITH ADVANCED CARCINOMA

Case No.	Patient	Plasma Fe[1]	Saturation[1] (%)	Fe Half-time[2a] (min.)	Plasma Fe Turnover[2b]		Red Cell Fe Turnover[2c]		Fraction of Plasma Fe Removed /hr.[2d]	Fraction of RBC Fe Renewed /day[2e]	Red Cell Mass (cc.)[3]	Plasma Volume (cc.)[3]	Per cent of Fe^{59} Utilized by RBC in 14 days[4]
					Mg./day	Mg./Kg./day	Mg./day	Mg./Kg./day					
1	A. A.	125	46	224	23.3	0.35	.....	....	0.25	.....	2052	3092	6
2	E. B.	91	39	106	27.6	0.5	27.6	0.5	0.37	0.02	1386	3400	26
3	E. D.	60	24	60	25.0	0.38	22.5	0.34	0.62	0.014	1680	2800	54
4	B. D.	100	27	150	15.4	0.31	9.2	0.19	0.28	0.014	660	2273	91
5	T. G.	76	54	68	23.5	0.52	5.4	0.12	0.70	0.009	597	1843	23
6	E. F.	49	17	49	31.0	0.35	46.4	0.53	0.68	0.011	3290	3860	42
7	C. H.	67	34	70	23.5	0.35	23.0	0.34	0.52	0.015	1508	2800	58
8	A. K.	89	27	117	21.1	0.30	25.3	0.35	0.31	0.009	2931	3306	41
9	F. L.	83	39	132	18.5	0.50	29.6	0.80	0.46	0.017	1705	2001	89
10	S. M.	90	38	75	47.8	.....	52.6	....	0.96	0.020	2600	2300	41
11	O. McK.	45	36	59	18.0	0.27	20.5	0.31	0.55	0.010	2010	3015	57
12	M. P.	50	24	70	21.4	0.26	25.7	0.31	0.58	0.010	2490	3410	50
13	R. S.	36	17	176	13.7	.....	10.7	....	0.86	0.013	828	1842	36
14	J. S.	44	28	88	31.7	.....	25.0	....	1.36	0.025	1000	2200	76
15	D. A.	43	22	38	31.2	0.46	61.5	0.90	0.94	0.309	1994	3278	92
16	B. R.	97	49	204	24.3	.....	3.4	....	0.44	0.005	705	2500	(11 D—19%)
17	S. B.	69	42	30	49.4	1.02	31.2	0.65	1.54	0.014	753	1935	58
18	A. B.	133	60	135	28.8	0.8	5.8	0.16	0.44	0.008	720	2000	25
19	L. L.	58	38	56	21.4	0.50	13.1	0.30	0.59	0.018	750	2570	(6 D—81%)
20	T. S.	45	29	42	26.4	0.49	62.1	1.17	0.96	0.036	1701	2552	107
21	F. W.	55	35	64	32.6	.....	22.9	....	0.62	0.013	1783	3973	32
22	J. R.	103	43	47	47.0	0.78	37.6	0.62	0.73	0.026	1462	2600	(13 D—54%)
23	D. S.	51	31	40	43.2	0.864	40.6	0.81	0.87	0.025	1638	2912	57
24	J. B.	110	61	112	26.2	0.51	6.6	0.13	0.43	0.009	725	1909	35
25	B. L.	107	53	132	14.2	0.23	12.6	0.20	0.21	0.008	1618	2640	58
26	S. F.	81	33	83	16.6	0.28	13.3	0.22	0.39	0.011	1180	2190	62
27	J. H.	35	11	122	8.9	.....	6.6	....	0.33	0.003	1938	2672	37
28	L. R.	85	32	150	9.4	0.18	4.7	0.09	0.21	0.003	1467	2200	54
29	P. G.	60	28	104	10.6	0.18	4.8	0.08	0.31	0.006	764	1700	57
30	M. M.	105	35	180	9.8	0.197	3.8	0.08	0.16	0.004	936	2417	(13 D—30%)
31	E. H.	75	29	146	195.4	.....	.....	....	2.46	.....	1717	4416	.....
32	M. W.	40	15	50	4.3	0.08	.....	....	0.17	.....	....	2592	61
33	A. L.	63	21	44	43.6	0.51	17.7	0.21	0.9	0.033	553	3132	72
34	G. C.	53	19	52	22.2	0.48	34.2	0.81	0.67	0.023	1468	2610	71
35	T. B.	114	36	110	17.5	0.33	10.9	0.20	0.33	0.010	1041	1933	(13 D—70%)
36	G. G.	93	30	86	53.3	0.80	42.1	0.63	0.70	0.025	1671	3394	(13 D—30%)
37	F. H.	63	21	55	30.5	0.47	.....	....	0.75	.....	....	2684	83
38	R. M.	124	40	38	94.1	1.88	177.8	3.55	1.38	0.14	1233	2290	83
39	E. D.	75	20	57	24.	0.67	.....	....	0.65	.....	....	2044	102
40	F. P.	60	27	64	21.8	0.31	28.6	0.40	0.51	0.012	2238	2967	50
41	C. G.	28	9	42	9.1	0.15	.....	....	0.42	.....	....	3222	62
42	B. T.	40	11	58	13.3	0.26	.....	....	0.60	.....	....	2302	(6 D—80%)
43	S. G.	73	19	58	31.7	0.63	.....	....	0.72	.....	....	2511	66
44	E. D.	37	10	51	14.5	0.29	.....	....	0.66	.....	....	2105	(13 D—63%)
45	J. G.	52	15	80	19.7	0.28	.....	....	0.55	.....	....	2843	(13 D—59%)

[1] Average of two or more determinations. Normal for plasma Fe/total iron binding globulin: 90–130 μg. per cent/260–350 μg. per cent. Normal plasma Fe saturation: 30 to 40 per cent.

[2] Normal values in this laboratory: (*a*) intravenous plasma Fe ½ time clearance: 60–120 min.; (*b*) plasma Fe turnover: 20–37 mg./day; (*c*) RBC Fe turnover: 14–38 mg./day; (*d*) fractions of plasma Fe removed/hr: 0.33–0.50; (*e*) fraction of RBC Fe renewed/day: 0.0072–0.0107.

[3] Calculated on basis of Fe^{59} studies—normal total blood volume approximately 77 cc./kg.

[4] Per cent of Fe^{59} administered intravenously appearing in RBC's 14 days after injection—normal 70–100 per cent.

disease, including a variety of blood dyscrasias, showed a further increase in the rate of destruction of normal donor cells. Thus the patients with carcinoma fell between this latter group and the normal.

the theory that erythropoiesis is normal or increased in the "average patient" with carcinoma. Since anemia develops in spite of normal or increased marrow function, apparently the demonstrated increase in hemolytic activity is

TABLE IV

IRON METABOLISM STUDIES IN FORTY-FIVE PATIENTS WITH CARCINOMA

Activity	Plasma Iron		Plasma Disappearance (rate)	Plasma Iron Turnover	Plasma Iron Removal (rate)	Red Cell Iron Turnover	Red Cell Iron Renewal (rate)	Red Cell Iron Utilization (14 days)
	Levels	Saturation (%)						
Decreased	31	23	19	16	9	14	5	14 (31%)
Normal	14	14	16	21	9	14	8	31 (69%)
Increased	0	8	10	8	27	7	22	.....
Total	45	45	45	45	45	35*	35*	45 (100%)

* Complete data not available in ten patients.

Marrow failure and/or replacement have been blamed for the anemia of patients with disseminated carcinoma. Our observations seem to justify a different interpretation. Normal cellularity was found in the great majority of instances even when tumor cells were present. In view of the limitation of morphologic technics attention was turned to the dynamics of iron metabolism.

The rate at which intravenously administered iron disappears from the plasma has been thought by some observers[11] to reflect the state of erythropoiesis in the individual. In these patients with carcinoma a great majority did have either increased or normal disappearance rates. These observations, therefore, would indicate normal marrow activity. However, since the iron disappearance rate may not necessarily reflect the status of erythropoiesis in patients with malignant disease, two other studies were performed. The first was the measurement of the red cell iron renewal rate per day. The second was the estimation of the percentage of Fe^{59} utilized in red cell production at a given time (for example fourteen days) following intravenous injection. These studies yielded further support to the theory that erythropoiesis is either normal or even increased in the majority of these patients. Thus it would seem that the direct and indirect evidence afforded by ferrokinetic studies, as well as that of the marrow morphology, support

greater than the marrow response in these patients. Clinical correlation with this theory is found in the common experience that frequent transfusions may be unsuccessful in maintaining adequate hemoglobin levels in advanced neoplastic conditions.

What factors are present in the plasma or the red cells of these patients with advanced carcinoma that lead to this increase of hemolysis provides a separate and complex problem in the metabolism of neoplastic disease which deserves further study.

SUMMARY

1. Forty-five patients with biopsy-proven, advanced carcinomas were selected for study of the pathogenesis of previously unexplained anemia.

2. Routine clinicopathologic tests revealed no significant increase in hemolytic activity.

3. The Ashby technic did demonstrate considerably increased rates of destruction in fifteen instances in patients with carcinoma, and in eleven instances in patients with non-carcinomatous neoplasm.

4. In the majority of patients studied normal marrow activity was found even in the face of marrow invasion by tumor cells.

5. Ferrokinetic studies with Fe^{59}, with special emphasis on intravenous plasma iron disappearance rates, red cell iron renewal rate and

percentage of Fe^{59} utilized for erythropoiesis also indicated a normal or increased state of erythropoiesis in these patients.

6. A major factor in the anemia of advanced cancer is an increase in hemolytic activity. In response to this increase in hemolysis the majority of these patients exhibited normal or increased erythropoietic activity which was, however, inadequate to prevent the development of anemia.

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Metastatic Tumors of the Heart*

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THE subject of metastatic tumors of the heart and pericardium has not provoked much interest in the past few years. This is because the incidence was generally considered low and clinical manifestations are the exception.

This report records the relevant findings in a group of autopsies conducted at the Veterans Administration Hospital, Hines, Illinois; in addition a few cases previously hospitalized there and examined at post mortem elsewhere are included. Records and follow-up data have been maintained by the Tumor Research Department of this hospital since 1931 on all hospitalized cases of malignancy.

From 1931 through 1951 more than 21,266 cases of malignant tumor have been treated at this institution. A total of 7,952 autopsies have been performed at this hospital, with the exception of a few elsewhere, and of this number of autopsies 4,124 had malignant disease. Not included in this group are benign tumors, brain and spinal cord tumors and leukemias.

The records of each case of cardiac and pericardial metastases have been reviewed as to pathology, symptomatology and laboratory data. In only a small number was the diagnosis made or suspected before death.

RESULTS

Incidence. The number of cases with heart or pericardial involvement totaled 217, approximately 5.0 per cent. Table I shows the incidence of individual types of tumor. Bronchogenic carcinoma and malignant melanoma show the highest incidence, the remainder are much less frequent. All cases were in males, as the female service at this hospital is very small. The age incidence was thirty to sixty-seven years, the greatest number falling between the ages of thirty-seven and fifty.

The heart was more often involved than the parietal pericardium but both were involved in a goodly number. Table II shows the distribution of these cases.

Spread. It is very difficult to determine the mode of spread accurately unless there is direct extension of the carcinoma from contiguous structures in the area, such as is often seen in bronchogenic carcinoma and occasionally in carcinoma of the esophagus. According to Scott and Garvin,[1] in their 118 cases reviewed at the Cleveland Clinic from 1919 to 1939, true embolic metastasis via coronary arteries was the most common mode of involvement of the heart. In view of the close proximity of the lymphatic trunks to the coronary vessels, according to the work of Rouvière[2] on lymphatic drainage of the heart, we would be inclined to believe that the greatest number of cardiac metastases were

TABLE I

Primary Tumor Metastasizing to Heart	Cases Autopsied (No.)	Heart and Pericardial Metastases	Percentage
Bronchogenic carcinoma	636	80	8.5
Malignant melanoma	76	23	30.3
Sarcoma (not lymph node)	240	14	5.8
Lymphosarcoma (no leukemia)	142	18	13.4
Carcinoma, metastatic, primary unknown	83	10	12.0
Kidney neoplasm (hypernephroma, carcinoma, pelvic carcinoma)	146	7	4.7
Esophageal carcinoma	183	9	4.9
Hodgkin's disease	189	8	4.2
Testicular carcinoma or teratoma	128	7	5.4
Colon carcinoma	144	4	1.6
Pancreatic carcinoma	148	4	2.7
Prostatic carcinoma	194	4	2.1
Adrenal carcinoma	24	3	12.5
Penile carcinoma	33	3	9.1
Gastric carcinoma	408	4	1.0
Parotid carcinoma and mixed tumor	34	3	18.9
Urinary bladder carcinoma	265	3	1.1
Rectal carcinoma	304	2	.7
Lymphoepithelioma	.....	2	....
Lip carcinoma	72	2	2.8
Breast carcinoma (male)	6	1	16.7
Tongue carcinoma	126	2	1.5
Alveolar ridge carcinoma	16	1	12.5
Branchial cyst carcinoma	8	1	12.5
Other carcinomas (respiratory passages, mouth, larynx, anus and thyroid)	424	0	0.0
Total	4,124	217	

* From the Veterans Administration Hospital, Hines, Ill.

due to lymphatic rather than hematogenous spread.

The importance of coincident metastases to the heart or pericardium or both, with involvement of other structures within the bony thorax is indicated in Table III. The primary site of the tumor was within the thorax in 116 cases, outside the thorax in ninety-one, and undetermined in ten instances.

Table IV indicates that involvement of heart and/or pericardium tends to be associated with rather widespread metastases of malignant tumors. In only eighteen instances were the metastases limited to the heart or pericardium.

Pathology. All cases in which the endocardium, myocardium and epicardium (visceral pericardium) were involved have been designated "cardiac" and only those tumors metastasizing to parietal pericardium have been termed "pericardial." Tables VI to IX summarize the gross pathologic findings encountered in our cases. In every case the microscopic features of the metastases corresponded to those of the primary tumor, except for occasional instances of necrosis.

TABLE II

Tumor	Total Cases	Metastases			Total Cardiac	Total Pericardial
		Pericardial Only	Cardiac Only	Both Pericardium and Heart		
Bronchiogenic carcinoma	80	26	21	36	57	62
Malignant melanoma	23	2	13	8	21	10
Sarcoma	14	2	7	5	12	7
Lymphosarcoma	18	2	11	6	17	8
Ca., primary undetermined	10	2	5	3	8	8
Ca. esophagus	9	..	6	3	8	3
Hodgkin's disease	8	1	7	1	8	2
Teratoma	5	1	3	1	4	2
Ca. colon	4	..	2	2	4	2
Ca. pancreas	4	..	3	1	4	1
Hypernephroma	5	..	5	..	5	...
Ca. prostate	4	..	3	1	4	1
Ca. adrenal	3	..	1	2	3	2
Ca. penis	3	..	3	..	3	...
Ca. stomach	4	1	2	1	3	1
Mixed tumor parotid	3	1	2	..	2	1
Ca. bladder	3	..	3	..	3	...
Ca. rectum	2	..	2	..	2	...
Ca. kidney	2	..	2	..	2	...
Ca. pelvis or kidney	2	..	2	..	2	...
Lymphoepithelioma	2	..	2	..	2	1
Ca. testicle	2	..	1	1	2	1
Ca. lip	2	..	1	1	2	1
Ca. breast	1	..	1	..	1	...
Ca. tongue	2	..	...	2	2	2
Ca. alveolar ridge	1	..	1	..	1	...
Ca. branchial cyst	1	1	...	..	...	1
Total	217	39	109	73	182	112

A total of 112 patients had involvement of the pericardium, and of these thirty-nine involved the pericardium alone. (Table II.) The classification in Table V shows the predominant mode of pericardial metastasis, although one type may grade off into the others. Bronchogenic carcinoma involved the pericardium more frequently than other primary tumor in this group, malignant melanoma did so infrequently. In about one-fourth of the cases increased pericardial fluid (Table VI) occurred without parietal pericardial involvement by tumor, and the incidence of bloody fluid was not as high

as might be expected in malignant disease of serous surfaces.

The gross pathologic findings in the cases with cardiac metastases were as variable as in those of the pericardium. Table VII lists the range of heart weight and shows that sixty-five hearts weighed over 350 gm.; of these, six were considered increased due to other types of heart disease. In many cases the heart weight was not listed, mainly because the heart was bound down with a large intrathoracic mass.

We have classified cardiac metastases according to location and distribution within the heart in Tables VIII and IX. As can be seen, diffuse cardiac metastases were approximately as frequent as localized masses. In seventy-two cases of the localized type (a single nodule or group of nodules) the site was specified and in these the left side of the heart predominated. Except when the heart was involved by contiguity the appearance of the tumor was generally nodular and pin-point, rice grain, or up to pea-sized. Usually the nodules were sharply circumscribed but in some cases were conglomerate and occasionally significant necrosis with softening occurred. Tumor nodules were generally situated in the epicardial region, some were in the myocardium, some in both, a few were predominantly in the endocardium. (Table IX.) An epicardial or endocardial tumor may bulge out from the surface, particularly the endocardial tumors which may encroach upon the contiguous heart cavity as a papillomatous propagation of tumor. In ten cases of

TABLE III
THORACIC STRUCTURES INVOLVED

	No. of Cases
One or both lungs or pleura	80
Mediastinal structures (mainly lymph node)	57
Both of the above	57
Other structures (ribs, chest wall)	7
No intrathoracic structures except heart	16
Total	217

TABLE IV

Metastatic Sites of Tumors Involving Heart and (or) Pericardium in Relation to Number of Organs, Excluding Regional Nodes	No. of Cases
To no organ or region except heart and/or pericardium	18
To only one other organ or region in addition to heart and/or pericardium	30
To two or more other organs or regions and heart and/or pericardium	169
Total	217

TABLE V

Types of Pericardial Metastases, Incidence	No. of Cases
Extension and attachment to mediastinal mass and pericardium alone	25
Extension and attachment to mediastinal mass and pericardium with extension to the heart	25
Pericardium studded diffusely with tumor nodules	12
Pericardium thickened and diffusely infiltrated with tumor	17
Pericardium thickened and diffusely infiltrated with tumor and with extension to epicardium and myocardium*	22
Pericardium infiltrated locally with tumor, without other attachment	11
Total	112

* Bronchogenic carcinoma accounted for twelve instances.

TABLE VI

Pericardial Fluid Encountered	No. of Cases
Simple effusion, over 100 cc.	15
Serofibrinous effusion	5
Purulent effusion*	4
Bloody pericardial fluid, 60 cc. and over†	21
Total	45

* A case of lymphosarcoma.

† Twelve of these cases bronchogenic carcinoma (largest bloody effusion 800 cc.).

predominate endocardial tumor growth, five papillomatous extensions into the heart cavity were noted; one of these formed a dumbbell-shaped tumor which grew from the wall of the right auricle, through the tricuspid valve into the right ventricle. Four of the endocardial

TABLE VII

Heart Weight (gm.)	No. of Cases
350 or under	123
Over 350*	65
Not given	29
Total	217

* Largest weights 850 and 780 gm.

tumors appeared to have been implanted directly upon the endocardium; the remaining six appeared to have originated from a myocardial nodule or to have extended directly from a primary bronchogenic carcinoma or mediastinal node. Epicardial metastases frequently showed a tendency to invade the myocardium, this being evident in practically every case

TABLE VIII

Location of Various Cardiac Metastases	No. of Cases
Right auricle	15
Right ventricle*	15
Left auricle	10
Left ventricle†	32
Diffuse tumor nodules or scirrhous type of thickening	78
Localized metastases, not specified	21
Microscopic involvement, no gross disease	6
Tumor thrombus in heart chambers	5
Total	182

* Total in right heart, thirty.
† Total in left heart, forty-two

microscopically. Involvement of the heart valves, chordae tendinae and septi did not occur frequently. (Table IX.) Tumor cells were not observed within the coronary arteries.

Of the sixteen cases with intracardiac involvement ten showed invasion of intraventricular septum. Valve leaflets were involved in three, papillomatous extension into the cardiac chambers occurred in five, and invasion of the papillary muscle was noted in two.

Extensive replacement of the myocardium was not frequent, the tumor acting more as a silent invader. Generally, sizable areas of apparently "healthy" myocardium remained, especially

TABLE IX

Situation of Cardiac Metastases	No. of Cases
Epicardium predominantly	78
Myocardium predominantly	32
Endocardium predominantly	16
Any combinations of above	35
Not mentioned	21
Total	182

with nodular involvement, even when diffuse. Usually the heart was not enlarged or deformed. When this occurred, it was due either to a rapidly growing tumor (as judged both clinically and pathologically) causing a massive, conglomerate, nodular growth or to a scirrhous, markedly fibrosing tumor involving the entire circumference of the pericardium and heart; these situations occurred in thirty-five instances. Malignant melanomas appear to be the most proliferative type of tumor metastasizing to the heart.

TABLE X

Clinical Manifestations	No. of Cases
Cardiac failure	17
Syncopal attacks	3
Murmurs	3
Pericardial effusion	4
Friction rub (pericardial)	2
Total	29

In addition to tumor, coronary arteriosclerosis was present in thirty instances but usually was mild. Myocardial fibrosis of moderate to marked degree, in addition to tumor, was noted in ten hearts. Other associated cardiac abnormalities were calcified aortic valve with stenosis two, aortic stenosis with insufficiency one, aortic insufficiency three, myocardial infarct two (recent), and unexplained cardiac enlargement one.

Symptoms. In general, symptoms referable

to the heart were absent. Cardiac failure was the most common (Table x), but in one case this was attributable to severe coronary arteriosclerosis with myocardial fibrosis (non-malignant). In only seven of the seventeen cases of congestive failure was this of such degree as to require

configuration in two, pericardial configuration (effusion) in five, displaced heart in one and progressively enlarging heart shadow in two. No reports of chest x-ray were available in a number of cases.

As to analysis of electrocardiograms, only

TABLE XI

Electrocardiogram	No. of Electro-cardio-grams	Site of Metastases						
		Diffuse Nodular	Inter-ven-tricular Septum	Right Heart	Left Heart	Peri-cardial Only	Peri-cardial and Myo-cardial	Other Types of Heart Disease
Normal limits	20	7	4	4	..	2	3	..
Abnormal, non-specific	20	4	1	2	1	5	6	1
Auricular fibrillation	1	1	..	..	..	..	..	..
Anterior coronary occlusion	1	1	..	..	..	..	..	..
Low voltage	6	2	1	1	..	..	1	1
Extra systoles	3	..	..	..	..	2	1	..
Intraventricular block	3	2	..	..	..	..	1	..
Left heart strain	2	..	..	2	1	..	..	1
Right heart strain	2	..	..		..	..	..	..
Pericardial effusion	4	..	..	..	..	2	2	..
Progressive ECG changes	3	1	..	1	..	..	..	1
Total ECG	65	18	6	10	2	11	14	4

intensive therapy. In one of the patients with syncopal attacks, auricular fibrillation at a rapid rate was apparently the cause; the two other cases were apparently due to interference in the conduction mechanism of the heart as there was no evidence of central nervous system metastasis and metastases were present in the interventricular septum and both auricles. A patient with a large tumor thrombus was moribund on admission and died within twenty-four hours. Pericardial effusion was proved by aspiration of bloody fluid. Evidence of tamponade was present in three.

Laboratory Procedures. Routine x-rays of the chest did not aid much in diagnosis. The essential findings were enlarged heart in ten cases, mitral

fifty-seven were taken. The types of electrocardiographic findings in relation to pathological findings can be seen in Table xi. Nonspecific changes predominated. In many of these cases the electrical activity in the heart was not altered despite extensive cardiac involvement by tumor.

Premortem Diagnosis. Seven cases of cardiac and/or pericardial metastasis were diagnosed prior to death. The diagnosis was made rather late in relation to onset of symptoms of malignancy, and in association with widespread malignant disease.

Mode of Death. All records were not complete in regard to the terminal symptomatology. There were seven sudden deaths and one suicide.

The remainder of patients gradually died of cachexia or some other complication of their primary tumor.

COMMENTS

The incidence of metastatic carcinoma of the heart has been variously reported as 0.5 to 19.1 per cent of all malignancies, excluding leukemias. At the time of Yater's article[3] in 1931, metastatic tumor of the heart was considered quite rare. Willis[4] reported an incidence of 6.2 per cent among 323 well studied autposies of tumors; Burke[5] reported fourteen cases in 326 autopsies; Lymburner[6] reported fifty-two cases from 8,550 autopsies of all types; Pollia and Gogol[7] had twenty-nine cases among 1,450 autopsies of malignancies; Herbut and Maisel[9] found forty-five cases in 409 autopsies of malignant tumors. More recent surveys give an incidence of cardiac metastasis of 3.4 per cent by Prichard,[10] while DeLoach and Haynes[11] found an incidence of 12.6 per cent, excluding leukemias. Bisel et al.[12] noted cardiac infiltration in 24 per cent of sixty-nine lymphomas and 12 per cent of 304 other tumors coming to autopsy. Cardiac involvement in leukemia may be as high as 44 per cent[12] in some series. Burnett and Shimkin[13] found an incidence of 14 per cent for metastasis to the heart in 209 tumor cases and an incidence of 29 per cent in leukemia. Young and Goldman[14] found an incidence of 19.1 per cent for such metastasis.

Pritchard[10] has listed certain factors which tend to decrease the incidence of cardiac metastasis: (1) the kneading action of the heart; (2) the metabolic peculiarities of striated muscle; (3) the rapid blood flow through the heart; and (4) the restricted lymphatic connections.

Bronchogenic carcinoma was the most frequently encountered primary tumor in our group and in the series of Scott and Garvin[1] and Herbut and Maisel.[9] Carcinoma of the breast was quite frequently mentioned in all papers but is not included in our study because of its limitations to males. Scott and Garvin's[1] results are also in agreement with ours in showing one-third incidence of bronchogenic carcinoma metastasizing to the cardiac structures. However, Ochsner's report[15] of 3,047 autopsies of bronchogenic carcinoma mentioned that cardiac and pericardial metastases occurred in 12.7 per cent. In other reports the most frequent primary mentioned is kidney, breast and lymph node.[3–6] In all reports sarcoma is a less frequent primary than carcinoma.

Malignant melanoma was frequently encountered in our study, a point stressed in several reports,[13,14,16] and was noteworthy for rapidity of growth in the heart and the marked replacement of functioning cardiac tissue. Practically any tumor can metastasize to the heart and pericardium.[1,3] Thyroid carcinoma has been considered rare, and we have no case; however there are reports of its occurrence.[3,17,18] According to Garvin,[19] Hodgkin's disease rarely implicates the heart. In our study, cardiac but not pericardial metastases were present in a substantial number. In the last few years four cases of Kaposi's disease (angioreticuloendothelioma) involving the heart have been reported.[20,21]

Metastasis to the heart alone is rare. (Table IV.) Willis[4] reports observations of Fergus that bilharzial cancer of the bladder caused a single metastasis to the heart in two cases and observations of Keynes concerning a single nodular metastasis to the myocardium which occurred as the only metastatic deposit of a primary renal carcinoma. Carcinoma of the duodenum[22] and sarcoma of the bladder[23] have been reported in recent years to metastasize solely to the heart.

MODE OF SPREAD

The mode of spread to the heart is frequently speculative but most observers[1,3,4,6,7,9,11] believe that the hematogenous route is the most frequent. Willis[4] has a most interesting chapter on this subject and points out that cardiac metastases are often missed at autopsy due to inadequate sectioning of the myocardium. Harrell[24] quotes a reference on the lymphatic supply of the heart and pericardium that shows many routes available for spread of tumor, particularly from mediastinal metastases. Mediastinal lymph node involvement by malignant disease greatly increases the chances of spread to the heart and pericardium, just as do pulmonary metastases.

The mode of spread to the heart is very difficult to establish unless there is direct extension of the carcinoma from contiguous structures in the area, such as is often seen in bronchogenic carcinoma and carcinoma of the esophagus.

The presence of a subendocardial and subpericardial lymphatic network is now generally agreed upon. The presence of lymphatic vessels or lymphatic capillaries in the myocardium, however, is still disputed. According to Rouvière[2]

the lymphatics of the heart may be classified as follows:

1. The subendocardial network: This network anastomoses with the myocardial lymphatic network. It also diverts its contents into the valvular collecting vessels which transverse the myocardium along the arteries.

2. The myocardial lymphatics: These networks communicate with the endocardial and, on the outer side, with the epicardial networks. In addition, they form in the myocardial substance valvular lymphatic vessels "which flow along and anastomose around the arteries which they accompany to the surface of the heart. Here they empty in the lymphatic collecting trunks of the cardiac sulci." This applies to the lymphatics of the ventricular myocardium. The existence of the lymphatic network in the auricular myocardium has not yet been proved.

3. The subpericardial or epicardial lymphatic network: The existence of this lymphatic network is accepted without dispute. The surface of the ventricles is covered by a rich lymphatic network which is more developed over the apex and the anterior and left lateral surfaces than on the diaphragmatic surface of the heart. This may well account for the large number of cardiac metastases found in the left ventricle. In the lymphatic network of the ventricular epicardium the lymph follows two main currents.

The left region of the epicardial ventricular network extends over the entire left ventricle as well as over that part of the right ventricle which is adjacent to the anterior longitudinal sulcus. The vessels of the anterior ventricular surface empty into two collecting trunks which ascend along the anterior longitudinal sulcus and the left coronary artery. The vessels from the inferolateral surface of the left region unite with two anterior trunks which emerge from the anterior longitudinal sulcus. From this union arises the left principal collecting trunk of the heart. The right region of the epicardial ventricular network covers the entire right ventricle except the portion adjacent to the anterior longitudinal sulcus which is drained by the left collecting trunk. Thus over their entire epicardial route the lymphatic trunks which collect the lymph from both lymphatic regions of the heart travel in company with the coronary vessels and in the fat which surrounds them. In most instances the lymph drained from the left principal collecting trunk is directed, by means of the tracheal bifurcation and the right laterotracheal nodes, to the right jugular subclavian junction. The lymph from the right principal collecting trunk is poured into the left jugular subclavian junction.

As mentioned, the right main stem of lymphatic drainage of the heart empties into the left anterior mediastinal nodes; this group of nodes also receives drainage from the diaphragm, liver, mediastinal pleura, lower thyroid gland and thymus, and passes it on to the right and left jugular subclavian junction. Therefore, tumor cells from one of these organs carried to the anterior mediastinal nodes may enter the cardiac lymphatics by retrograde flow. The left main lymphatic stem of the heart drains into the nodes at the tracheal bifurcation or into the anterior mediastinal node. The tracheal nodes receive drainage from the lower part of the trachea, the bronchi, lungs and esophagus. Carcinoma in any of these organs might metastasize to the heart by retrograde lymphatic spread through the left main lymphatic stem.

It is also well known that when chronic adhesions form between the visceral and parietal pleura, lymphatic vessels grow across and connect the lymphatics of the lungs with these of the chest wall, diaphragm or pericardium. This probably accounts for the large number of cases of bronchogenic carcinoma with extension to the heart.

Recent studies of the direction of the stream as well as the distribution of the valves in the cardiac lymphatics have revealed significant findings. No valves were found in the myocardial lymphatics but they were present in the epicardium. Such valves are more numerous on the anterior surface than the diaphragmatic surface of the heart and are very uncommon in the auricle.

PATHOLOGY

The pathology of cardiac and pericardial metastases is adequately covered by Yater,[3] Willis[4] and Herbut and Maisel.[9] Our findings are in accord with these descriptions. An interesting type of spread from bronchogenic carcinoma which did not occur in our series is that of propagation of the tumor via a pulmonary vein directly into the left auricle, possibly with further extension into the left ventricular cavity.[25–27]

There has been some division of opinion as to which side of the heart tumors are more likely to metastasize, the right,[3,10] left[1,14] or diffusely.[9] Probably the reason for this variation is the types of primary tumor most often encountered

in a particular series. In this series, in which bronchogenic carcinoma was most frequent and tumor spread more often hematogenous via pulmonary veins, it is not surprising that left heart involvement was more common.

CLINICAL MANIFESTATIONS

Generally, no clinical findings are present unless cardiac metastases are extensive. Cardiac failure or conduction disturbances (usually detected in the electrocardiogram) are the most common clinical manifestations. It is apparent that metastatic tumor to the heart or pericardium may give rise to symptoms as the result of one or more of the following conditions: (1) invasion of the myocardium with replacement, leading to congestive failure; (2) interference with coronary flow, leading to angina pectoris or congestive failure and possibly infarction; (3) distortion of the cardiac valves; (4) intracardiac obstruction by new growth; (5) disturbance of rhythm or conduction; (6) compression of the heart by fluid or diffuse invasion of the pericardium; (7) rupture of the myocardium; (8) embolism originating in tumor thrombi. It is remarkable that so few clinical manifestations develop, even with severe destruction and replacement of cardiac muscle. Lisa and others[28] point out other findings that do occasionally occur, namely, valvular disease resembling mitral stenosis, anginal pain and Stokes-Adams syndrome. According to these authors there are no diagnostic signs or symptoms; however, the onset of cardiac dysfunction in the presence of widespread malignancy or intractable cardiac failure of obscure cause should make one suspect the presence of tumor in the heart.

Pericardial metastases are usually silent, more so than myocardial tumors, and pericardial effusion is the significant clinical finding.[7,29] Aspiration should be performed and the sediment studied for tumor cells. Hemorrhagic fluid is significant but was present in only twenty-one of forty-five patients in this series. Constrictive pericarditis may result from pericardial metastases.[30,31]

Electrocardiograms may be normal with considerable myocardial involvement and only occasionally reveal diagnostically helpful information, according to our experience. This is borne out by Siegel and Young[32] who state there is no uniformity of findings; their most common abnormality was a variable inversion of T waves and low voltage. Coronary infarction patterns have been reported,[32,33] also disturbances in conduction and arrythmias.[35,36]

X-ray of the chest has rarely been helpful in diagnosis in our series. In reviewing the literature, the x-ray findings were rarely of diagnostic significance. Pericardial effusion and cardiac enlargement are the most important findings.

Doane and Pressman[37] summarized all cases of metastatic malignancy of the heart to be diagnosed prior to death; there were twenty cases to that date. In 1947 Brick and Greenfield,[38] in a survey to that date, found twenty-two instances of antemortem diagnosis of tumor of the heart. Four of these were primary tumors. To this series they added one case of reticulum cell sarcoma diagnosed before death. Later, instances of antemortem diagnosis of metastasis from carcinoma of the cecum[39] and malignant melanoma were added.[40] Dimmette[41] in 1950 reported four instances in which the antemortem presumptive diagnosis of metastasic lesions of the heart was made. DeLoach and Haynes[11] added two more such instances, as did Burnett and Shimkin.[13] The antemortem diagnosis was made seven times in this series of cases.

Death usually is referable to complications of tumor other than the metastases to the heart, namely, cachexia, hemorrhage, infection and the like. This was noted in our group and in articles mentioned. In the past, sudden death has been regarded as fairly frequent but this was not apparent in our cases. There are occasional cases with sudden death due to Stokes-Adams syndrome and ball-valve action of obstructing tumor thrombi. We have not met with acute embolic phenomenon of tumor masses from the heart. One patient was reported to have died of cardiac rupture.[22]

SUMMARY

An analysis of the findings in 217 cases of neoplasm with cardiac and pericardial metastases is presented. The clinical and autopsy data are correlated.

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Association of Gastrointestinal Carcinoid Tumor with Cardiovascular Abnormalities*

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A SYNDROME of malignant intestinal carcinoid with hepatic metastases and fibrostenotic lesions predominantly of the pulmonic and tricuspid valves has recently been described. Isler and Hedinger[1] reported three of their own cases and commented on another. The three cases were individuals in the fourth, fifth and sixth decades. All had clinical evidence of right-sided heart failure with dyspnea, cyanosis, neck vein distention, peripheral edema and cardiac murmurs. At postmortem examination carcinoid tumors of the small intestines were present. These had metastasized extensively to the liver. In two instances there were fibrostenotic changes in the pulmonic and tricuspid valves together with a more diffuse endocardial fibrosis. In the third case the valvular lesion was described as a form of "chronic recurrent verrucous endocarditis." In one case there was also some involvement of the mitral valve. Rambo, Gore and Vance[2] described another case with essentially the same clinical and autopsy findings. They postulated that the valvular alterations might perhaps have developed secondarily to some biochemical effect on the endocardium produced by a substance liberated by the carcinoid tumor tissue.

In order further to evaluate the incidence and pathogenesis of this syndrome twenty-six autopsied cases of carcinoid tumors of the gastrointestinal tract, derived from an autopsy series of 8,000 adults, were analyzed. In reviewing these cases particular attention was directed to any developmental or acquired cardiovascular defects, the primary site and size of the carcinoid tumors, and the extent and distribution of the metastases. In addition, 500 autopsies sampled at random from the entire series of 8,000 were also studied relative to the presence of developmental cardiovascular defects and fibrostenotic lesions limited to the pulmonic and tricuspid valves. In both groups of cases, those with carcinoid and those without, such findings as probe patency of the foramen ovale, fenestrations of the semilunar valves and minor accessory coronary orifices were ignored. The incidence of these alterations was the same in both groups and was in keeping with well established figures.[3]

The observations concerning carcinoid tumors, metastases and cardiovascular abnormalities are presented in Table 1.

In the 500 autopsies on adults without carcinoid tumors, less than fifty (10 per cent) showed any developmental defects of the heart (excluding the abnormalities mentioned previously). In contrast to this, in the twenty-six cases with carcinoid tumors there were nine (33 per cent) with unequivocal congenital defects or anomalies. In the control group there was not a single instance of isolated fibrostenotic involvement of the tricuspid and pulmonic valves. These valves were involved only in cases of rheumatic heart disease, in conjunction with involvement of the valves on the left side of the heart. In the cases with carcinoid tumors there were ten with varying degrees of right-sided valvular lesions; in none of these were there any stigmata of rheumatic heart disease. All told, eighteen of the twenty-six cases exhibited some cardiovascular abnormality or defect.

Among the defects were two hearts with true Chiari's net. The reported usual incidence of this finding is once in 500. Dextrocardia with an atretic right auricle and a pulmonic valve with four cusps are not very common anomalies yet these were present in this small group of cases. The incidence of the isolated tricuspid and pulmonic valvular changes appears even more significant.

Among the twenty-four cases in which the carcinoid was primary in the intestinal tract

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TABLE 1

Autopsy No.	Age and Sex	Primary Site of Carcinoid	Sites of Metastases	Cardiovascular Abnormalities
9745	41, M	Ileum	Liver, mesentery, lymph nodes	Hyaline nodules on anterior pulmonic valve cusp
10101	55, M	Ileum	None	Dextrocardia; thin-walled right auricle
10972	61, M	Ileum	Liver, lungs, pleura, lymph nodes, thyroid	Edematous thickening of tricuspid valve; subpulmonic valve; endocardial fibrosis
11651	66, M	Ileum	Liver, heart, lymph nodes	Marked sclerosis of pulmonic and tricuspid valves; hypertrophy of right ventricle; aortic arch malformation
11877	72, M	Ileum	Lungs	Endocardial fibrosis, right ventricle; extensive scar below pulmonic valve
12443	47, F	Ileum	Liver, lungs, spleen	Marked sclerosis of pulmonic valve with distortion; moderate fibrosis of tricuspid valve
13025	65, F	Ileum	None	Chiari's network; coronary sinus valve
13070	42, F	Rectum	None	Anomalous aortic arch
13237	43, M	Rectum	None	None
13599	46, M	Ileum	Liver, lymph nodes	Tricuspid and pulmonic valve sclerosis, marked; anomalous aortic arch
13733	64, M	Ileum	None	None
13827	70, M	Stomach	None	Chiari's network; moderate fibrotic thickening of tricuspid valve
14480	63, M	Ileum	Lymph nodes, ovary	None
14695	46, F	Ileum	Liver, pleura, lymph nodes	Widely patent foramen ovale
14880	55, M	Ileum	None	Widely patent foramen ovale
14934	42, F	Ileum	None	None
14961	70, M	Ileum	None	Separate left circumflex artery arising from aorta
14966	68, F	Ileum	Lymph nodes	None
15243	38, M	Cecum	Liver, lungs	None
15313	81, M	Ileum (multiple)	None	Four pulmonic cusps
15322	54, M	Ileum	None	None
16572	60, F	Ileum	None	None
17049	64, M	Ileum	None	Focal scarring of endocardium, both ventricles; sclerosis of mitral valve
9839	66, M	Ileum	None	Fibrotic thickening of tricuspid valve with roughening of edge of infundibular leaflet
11386	44, F	Appendix	None	Edematous thickening of tricuspid valve; widely patent foramen ovale
11495	64, M	Appendix	None	None

(excluding the two appendiceal cases) were ten with metastases. This finding is in general agreement with the experience of others.[4] There was a notable difference, in the distribution of the cardiovascular lesions, between those with and those without metastases. Seven of the ten cases with metastases demonstrated endocardial fibrosis with involvement of the pulmonic and tricuspid valves. Only three of the sixteen without metastases had any of these alterations. The other defects were more common in the cases without metastases.

The endocardial changes varied in age, severity and extent. In some there was minimal fibrotic thickening which was diffuse or focal; in others it was extensive and resulted in marked anatomic distortion of the valves. In some instances the valves exhibited an earlier and edematous type of involvement. In one case a fresh non-bacterial thrombotic or verrucous type of endocarditis was superimposed upon a scarred valve. In a few instances there was fibrosis, at times extensive, in the endocardium beneath the pulmonic valve ring. In one case mitral valve involvement also was present. The older and more advanced changes were found in those cases in which the carcinoid had metastasized; however, advanced changes were not necessarily limited to those with extensive hepatic metastases.

DISCUSSION

It is quite clear that the syndrome is not merely a coincidence of conditions. There is no ready explanation for the differences in the cardiovascular findings in those cases with metastases and those without. However, because of the high incidence of developmental cardiovascular alterations in the group as a whole, and because there is justification for regarding carcinoid tumors as being developmental in origin, it is possible that there is a basic defect in the valvular substance which during life may progress to marked valvular damage.

Rambo, Gore and Vance advanced the concept that the progressive and acquired changes in the valves may be related to some substance derived from the tumor tissue which exerts a deleterious effect on the endocardium. The discharge of this material into the right side of the heart, particularly if derived from liver metastases, might account for the predominance of the changes in this area. The carcinoid tumor is thought to originate from the Kultschitzky cells which by some are claimed to have a neuroendocrine function.[5] Pernow and Waldenstrom[6] have recently demonstrated the presence of substances resembling 5-hydroxytryptamine (serotonin) during attacks of flushing in the blood and urine of two patients with carcinoid tumor. They also indicate that there is sufficient evidence now to be certain that this substance, or substances similar to it, are secreted by the intestinal argentaffin cells. They also quote a report by Lembeck who has recently found that benign carcinoid tumors contain large amounts of 5-hydroxytryptamine. This would support the concept of Rambo, Gore and Vance. The progression of the lesion on the valves may also be dependent on recurrent episodes of a non-bacterial thrombo-endocarditis with subsequent scarring. Such a lesion was observed in one of the cases in this group and another was reported by Isler and Hedinger.

Other instances of the association of developmental neoplasms with non-neoplastic anomalies are known. One such example would be the association of congenital rhabdomyoma of the heart and renal cysts with tuberous sclerosis. Evidence for the developmental origin of carcinoid tumors is found in the early age at which they are observed in the appendix; their frequent and characteristic location near the tip of the appendix; the multiplicity of primary sites in individual cases; and the peculiar type and rate of growth.

Since patients with carcinoid may survive for many years even with extensive metastases there is time for the valvular lesions to develop to the extent that they may be recognized clinically. Perhaps biochemical study of these cases, as suggested by others, may provide an explanation for the progression of the basic developmental cardiovascular defect.

It should be noted that the valvular changes, at least in their end stages, are anatomically indistinguishable from those that may occur in rheumatic heart disease.

SUMMARY

1. Carcinoid tumors of the gastrointestinal tract appear to be associated with a high incidence of cardiovascular abnormalities.

2. In addition to cardiovascular developmental defects or anomalies, acquired endocardial lesions predominantly involving the tricuspid and pulmonic valves are frequently present.

3. The most advanced involvement of the tricuspid and pulmonic valves is found in those cases in which the carcinoid tumor has metastasized.

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Dermatomyositis: Diagnostic Features and Therapeutic Pitfalls*

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It is the purpose of this report to describe two cases which (1) highlight the value of urinary creatine determinations and muscle biopsy in arriving at a diagnosis of dermatomyositis, (2) conversely, delineate the clinical features of dermatomyositis which make possible a positive diagnosis in the face of incomplete laboratory confirmation, and (3) illustrate hazards which beset ACTH-cortisone therapy in this disease.

Dermatomyositis, the rarest of the so-called collagen diseases,[1] was first described in 1863 by Wagner.[2] Scheuermann[3] was able to review 263 cases in 1939 and the number of reported cases is now in the vicinity of 600.

Dermatomyositis is difficult to define with precision because it is primarily a clinical entity, with little pathologic or biochemical distinctiveness. In 1922 Steiner[4] described it as "an acute, subacute or chronic disease of unknown origin characterized by a gradual onset, with vague or indefinite prodromes, followed by edema, dermatitis and a multiple muscle inflammation." This was modified in 1935 by Sydenstricker and Thomas[5] to read "non-suppurative muscle inflammation."

It is now possible to describe dermatomyositis more exactly as a collagen disease in which non-suppurative polymyositis with creatinuria is the distinguishing characteristic, commonly accompanied by dermatitis and edema. Emphasis on creatinuria in dermatomyositis is justified because in no other collagen disease is this abnormality so striking and so consistent.

CASE REPORTS

CASE 1. A fifty year old retired Master Sergeant first sought medical aid at the Reno Veterans Administration Hospital, July 11, 1953, because of pain in the right shoulder. The shoulder area was injected with procaine for relief of "bursitis." The next day dyspnea and right chest pain developed which proved to be due to pneumothorax. The patient was hospitalized for thirty days and the lung expanded satisfactorily. Studies for tubercle bacilli were negative.

After leaving the hospital he was asymptomatic until August 22, 1953, when pain in the right shoulder recurred, followed in the next two weeks by migratory polyarthritis involving the shoulders, hands, knees and back. Intermittent swelling without redness was present in the peripheral joints. Five days prior to admission a cough productive of thick white sputum developed.

On admission to the hospital, September 10, 1953, the patient was almost immobilized by severe articular pain. Physical examination showed swelling of the wrists and signs of pleural fluid in the right chest. Initial laboratory studies showed normal urine, leukocyte count, hemoglobin and sedimentation rate (4 mm./hr., Wintrobe). Chest roentgenograms showed fluid covering the lower one-third of the right lung field and a hazy infiltrate in each apex. (Fig. 1.) He was able to produce only one scanty twenty-four-hour sputum sample; this and three gastric washings were negative for tubercle bacilli. Second strength tuberculin (PPD) was positive.

His cough and expectoration cleared up within a week without therapy. Within four weeks the pleural reaction subsided with minimal residual thickening, and the apical densities disappeared. In the meantime arthritis became the dominant feature of his illness. Joint pain became less migratory and more persistent, and periarticular thickening about the shoulders, wrists,

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metacarpophalangeals and knees progressed at an alarming rate. About the tenth hospital day it was noted that weakness of the distal muscles of the upper extremities was developing, quite out of proportion to the severity and duration of his arthritis. The muscle bellies were not swollen or tender but atrophy was evident. Effusion appeared in the right knee and moderate edema of the ankles developed. Pale amber fluid, 20 cc., was aspirated from the right knee and showed 2,800 leukocytes per cu. mm. of which 1 per cent were eosinophils. The serum uric acid was 2.3 mg. per cent, the serum NPN 35 mg. per cent, the serum albumin was 2.7 gm. per cent and the serum globulin 3.7 gm. per cent. The sedimentation rate rose to 52 mm. per hour. A serum test for L.E. cells was negative.

A tentative diagnosis of dermatomyositis was made.

Urinary excretion of creatine was found to be 780 mg. per twenty-four hours. (Table 1.) Biopsy of the right gastrocnemius muscle was reported to show: "several fragments of skeletal muscle fibers; in several areas there are degenerative changes. The interstitial vessels show a diffuse chronic inflammatory infiltrate in perivascular regions. This infiltrate consists of lymphocytes and monocytes. In an occasional area inflammatory cells are noted in the wall and within the lumen of the vessels. A larger area reveals a diffuse chronic inflammatory process between fragments of eosinophilic amorphous staining material, suggesting degenerative skeletal muscle fibers and collagen bundles. This process is similar to those around the vessels, but in addition there are plasma cells and cells with pale nuclei suggesting reticulum cells. The vessels in this area show marked degeneration of their walls, with eosinophilic hyaline material within the lumen. There is an absence of granulation tissue, neutrophils and eosinophils. Diagnosis: Dermatomyositis, gastrocnemius muscle, right."

By the fourth week in the hospital fibrous ankylosis of the involved joints was detectable despite the use of salicylates and physiotherapy. Hydrocortone, 20 mg. q.i.d., was started orally on the thirty-fourth hospital day, with prompt relief of pain and stiffness. However, periarticular thickening and limitation of motion were only slightly ameliorated. The erythrocyte sedimentation rate fell to 11 mm. per hour, and the serum albumin was 3.3 gm., globulin 3.1 gm. per 100 ml. As can be seen from Table 1, a gratifying drop in urinary excretion of creatine occurred. To our chagrin, however, this change toward normal occurred three days *before* hydrocortone was started.

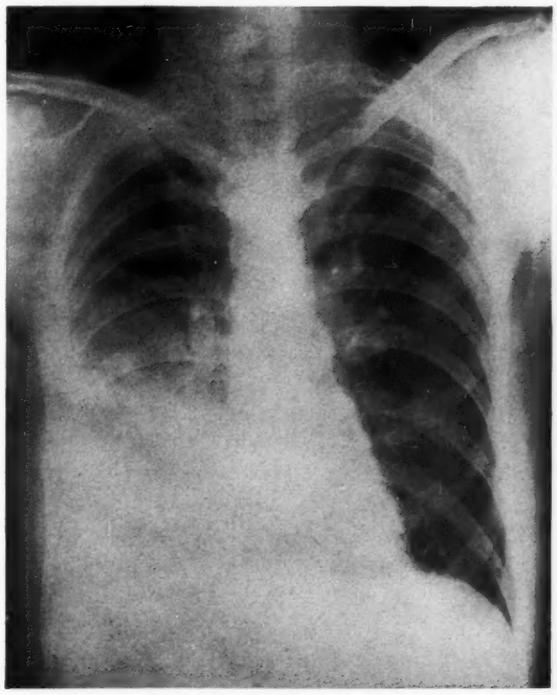


FIG. 1. Case 1. Right pleural effusion and bilateral apical infiltrations present at the time of first admission to hospital.

Although he had been bedridden before beginning treatment, the patient became hyperactive after starting hydrocortone. He had insomnia and was alternately euphoric and bellicose. At his insistence he was released from the hospital on the nineteenth day of hydrocortone therapy.

Outpatient follow-up November 17, 1953, showed continued improvement. On December 1, 1953, cortisone, 67.5 mg. per day, was substituted for hydrocortone and gradual withdrawal of the hormone was begun. On December 15 he complained that pain and stiffness in his wrists and knees were accentuated. The effusion in his left knee had recurred and fibrous ankylosis of his shoulders had progressed to the point where abduction was limited to about 25 degrees to each side. He complained of "heartburn" and an episode of nocturnal vomiting. He vigorously denied ever having had any gastrointestinal symptoms prior to his present illness. Because of the danger of a cortisone-induced peptic ulcer, antacid medication was started and the dose of cortisone was further reduced to 50 mg. per day.

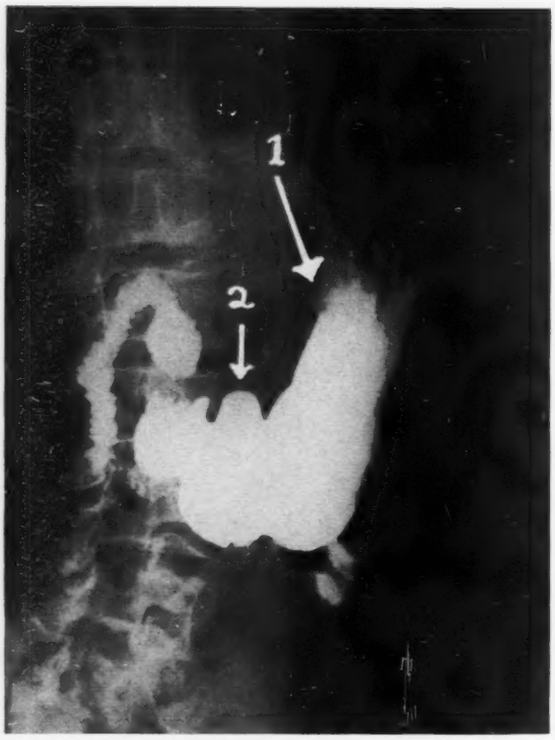


FIG. 2. Case 1. Small ulcer (1) high on lesser curvature of stomach, and (2) large prepyloric ulcer which simulates a peristaltic wave but on fluoroscopy was fixed and failed to transmit peristalsis.

His epigastric distress worsened and on December 28, 1953, he vomited approximately one quart of coffee-ground material and passed two tarry stools. He was admitted to the hospital in shock, which responded to transfusions. An upper gastrointestinal series three days later showed a large ulcer crater on the pyloric portion of the lesser curvature of the stomach. A second ulcer, considerably smaller, was later demonstrated higher on the lesser curvature. (Fig. 2.) The patient left the hospital against advice on the eighth day. He adhered to an ulcer regimen and roentgenograms of the stomach showed progressive healing of both gastric ulcers, with complete disappearance by March 10, 1954.

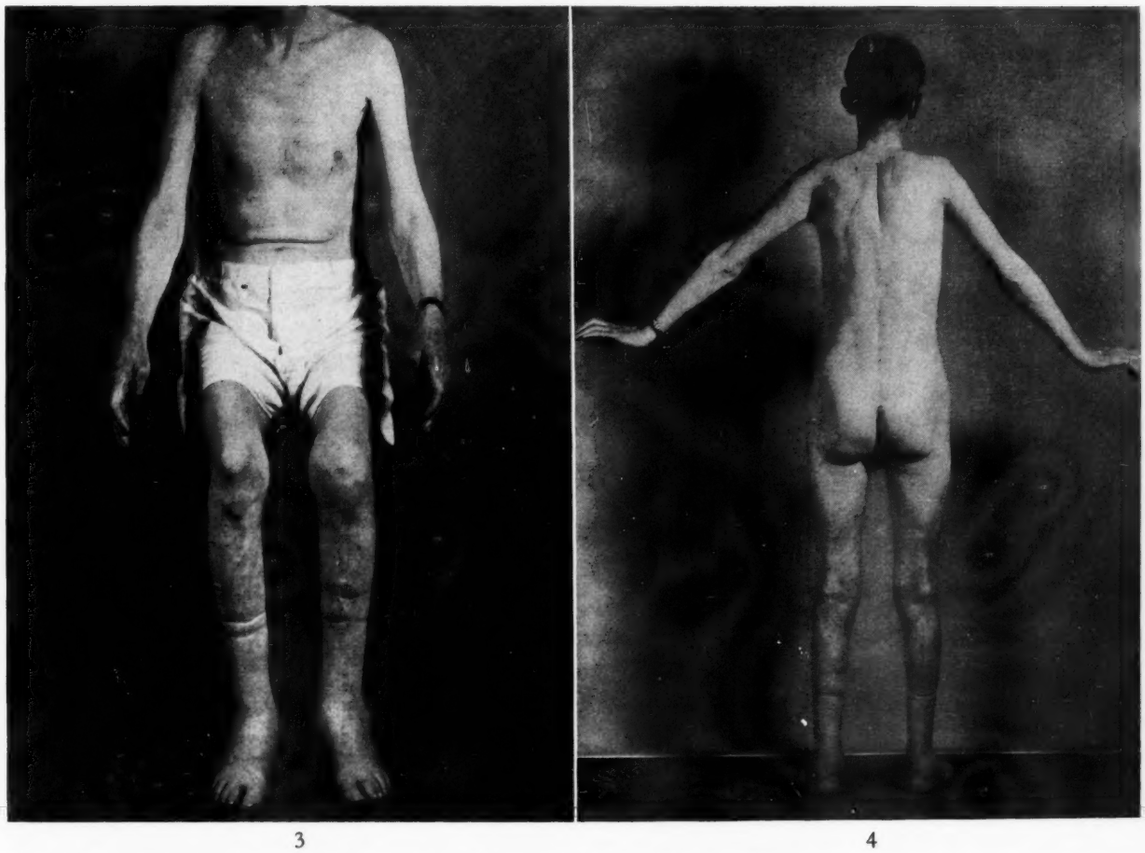
Cortisone was stopped at the time of his hematemesis, and his stiffness progressed: motion of his mandible was restricted to approximately 15 degrees, and he could no longer close his fingers into a fist. Atrophy of the calf, shoulder and interosseous muscles of the hands was pronounced. Fasciculation of the muscles of his upper back was noted. His gait was slowed to a shuffle by pain across the dorsa of his feet and persistent edema of his feet and ankles. Excretion of creatine dropped briefly to normal (February) after discontinuation of cortisone but then resumed the level which had been present before steroid therapy. (Table 1.) Mixed tocopherols (50 mg. twice daily) and testosterone propionate (25 mg. intramuscularly twice weekly) were administered for the next three months, during which time slow but unmistakable improvement in muscular strength and joint mobility occurred. Figures 3 and 4 illustrate the muscular atrophy, edema and articular changes present at this time.

TABLE 1
TWENTY-FOUR HOUR CREATINE* AND CREATININE EXCRETION (CASE 1)

Date	Creatine* (mg./ 24 hr.)	Creatinine (gm./ 24 hr.)	Urine Volume (cc./24 hr.)
Sept. 21, 1953	780	2.5	2600
Oct. 12, 1953	600	2.65	2805
Oct. 19, 1953	222	2.1	1800
Oct. 28, 1953	272	1.7	1800
Nov. 3, 1953	238	1.76	1925
Nov. 8, 1953	232	1.6	1980
Nov. 19, 1953	134	1.2	1875
Dec. 28, 1953	267	1.7	2230
Feb. 10, 1954	85	1.7	1200
Mar. 10, 1954	464	2.2	1750
Apr. 27, 1954	209	1.5	1480

* Method of creatine determination. Hawk, P. B., Oser, B. L. and Summerson, W. H. In: Practical Physiological Chemistry, 12th ed., p. 509. Philadelphia, 1937, P. Blakiston's Son & Co. The normal range is 0–200 mg./ diem.

In this case a collagen disease was first suggested by the coexistence of pleural effusion and arthritis. A negative L.E. cell test ruled out systemic lupus erythematosus, and the rapid development of persistent joint damage excluded rheumatic fever. The arthropathy was typical of rheumatoid arthritis but this was not considered to be the definitive diagnosis because: (1) muscular weakness and atrophy developed with unusual rapidity and severity, and (2) the disease began with pleuropulmonary involvement. Visceral lesions may occur in rheumatoid arthritis but usually late in the disease and they are often subclinical, being discovered at autopsy. A great variety of serious visceral manifestations has recently been reported in patients with rheumatoid arthritis, including pleuritis, pneumonitis, pericarditis, pathologic



3 4

FIG. 3. Case I. Involvement of wrists, hands, ankles and left knee. Edema of legs.

FIG. 4. Case I. Mild to moderate atrophy of muscles of legs, upper back and shoulder girdles. Shoulders and wrists are maximally extended, showing degree of ankylosis ten months after onset of illness.

findings of periarteritis nodosa[6] and false positive serum L.E. tests,[7] following treatment with cortisone. The pleuropulmonary lesions in our patient appeared concomitantly with the joint symptoms and before cortisone was administered.

Confirmation of the diagnosis of dermatomyositis was afforded by the marked creatinuria and by muscle biopsy. This patient's persistent failure to develop dermatitis is unusual but similar cases of dermatomyositis have been reported.[8]

The two gastric ulcers in this patient were probably secondary to steroid therapy. The fact that he had had no gastrointestinal symptoms prior to ingesting hydrocortone and cortisone, and the healing which followed withdrawal of the hormones support this conclusion. The possibility remains that the ulcers resulted from dermatomyositic involvement of the submucosal blood vessels with infarction of the gastric mucosa. Gastrointestinal ulceration on this basis has been demonstrated at autopsy in dermatomyositis.[9]

CASE II. A twenty-two year old housewife was admitted to the hospital September 22, 1953, complaining of a skin rash. The eruption began on August 15th with a few small papules on the left wrist. Three days later penicillin, 300,000 units t.i.d., was given at another hospital in conjunction with a minor operation on the urethra. The following day an eruption on her breasts developed which within a week spread over her entire body, sparing only the face and back. On admission she presented many large scaling plaques (3 to 8 inches in diameter) which were dry and intensely pruritic. The plaques had raised edges and no central clearing. The scale was white, hard and adherent. There was no ulceration or mucous membrane involvement. All lymph nodes accessible to palpation were moderately enlarged and slightly tender.

Past history revealed no previous allergic phenomena and was otherwise non-contributory.

Initial laboratory studies, including urinalysis, complete blood count, serologic tests and chest roentgenogram were normal. A consulting dermatologist reported a punch biopsy of the skin as "negative," and suggested a tentative diagnosis of penicillin reaction. Neurodermatitis was considered because of the fact that one month before her rash appeared the patient had witnessed the death of one of her children in an automobile accident.

Response to antihistaminics and topical therapy was poor, and she was given ACTH by intravenous drip for four days and then intramuscularly for eight days. There was doubtful improvement and therapy was changed to cortisone for one week in decreasing dosage. Her temperature reached 100°F. on three occasions. At the time of dismissal on the twenty-second day there was slight improvement in her skin. She remained at home only five days. Although her dermatitis became much worse, her readmission was actually prompted by muscular rather than cutaneous symptoms. During her first hospital stay she had complained of a great deal of back pain, and the paraspinal muscles were remarkable tender to palpation. At that time the significance of this observation escaped us. After she left the hospital similar pain appeared in her arms and legs. All of the involved muscles developed an inordinate degree of weakness in a short time and on readmission to the hospital the patient was unable to walk because of pain and weakness in her legs.

Examination showed that she was acutely and severely ill, with a temperature of 103.6°F. Her body was covered from scalp to toes with a dry exfoliation, severely pruritic, and the underlying skin in a few areas showed purplish mottling suggestive of small ecchymoses. Mild edema, both subcutaneous and intracutaneous was present over the entire body, most pronounced periorbitally. The muscles of her back and extremities were exquisitely tender to pressure. The lymphadenopathy previously noted was accentuated. There was tachycardia (120/min.) and a systolic murmur grade II in the pulmonic area.

Urinalysis and complete blood count were again normal, without eosinophilia or lymphocytosis. Fluoroscopy of the chest showed that the cardiac silhouette was somewhat more globular than before, and the amplitude of cardiac pulsations was diminished, suggesting pericarditis. An electrocardiogram showed right axis deviation, low amplitude QRS in Lead I, aVR and aVF, T waves upright in Lead I, inverted in Lead III and flat in aVF. The transition zone appeared in lead V_5. A second electrocardiogram seven weeks later was normal.

TABLE II
TWENTY-FOUR HOUR CREATINE AND CREATININE EXCRETION (CASE II)

Date	Creatine (mg./24 hr.)	Creatinine (gm./24 hr.)	Urine Volume (cc./24 hr.)
Oct. 22, 1953	465	2.0	1600
Nov. 2, 1953	279	1.26	1860
Nov. 4, 1953	162	1.1	1250
Nov. 17, 1953	1680	1.73	2650
July 2, 1954	168	1.6	1400

A tentative diagnosis of dermatomyositis was made.

Urinary excretion of creatine the day after her second admission was 465 mg. in twenty-four hours. (Table II.) Biopsy of the skin and right gastrocnemius muscle three days after admission was reported to show "intact muscle fibers separated by loose mildly vascular fibrous connective tissue. A moderately thickened, parakeratotic epidermis which exhibits mildly elongated club-shaped rete pegs, a thin granulosal layer, and frequent cells showing intracellular edema. A few small aggregations of segmented neutrophiles are present within the parakeratotic lamina. The vascular dermal papillae are elongated, extend close to the surface, and contain scattered lymphocytes, occasional segmented neutrophiles, and a few melanin laden macrophages. The underlying dermis exhibits many capillaries cuffed by lymphocytes. Diagnosis: Skeletal muscle, no diagnostic features; dermatitis, chronic, nonspecific."

ACTH was reinstituted October 23rd immediately after the biopsy. Within four days fever subsided and she was able to eat and sit up in bed. Exfoliation continued however at a brisk pace. Raw fissures appeared in the flexural creases under the breasts, at the elbows and groins. She complained bitterly of a feeling of tightness in her skin and refused to move for fear her skin might crack open. The itching and dryness could be controlled only by keeping her swathed from head to toe in lanolin dressings. Despite all efforts she shed great quantities of skin and lost weight steadily.

A second dermatologic consultation was obtained, and a third biopsy was taken from the right deltoid area. This was reported to show features "highly suggestive of psoriasis, which can occasionally exfoliate." Urine analysis for arsenic was negative. A serum test for L.E. cells was negative on two occasions. The serum protein-bound iodine was 6.6 μg. per 100 cc., NPN 28 mg. per cent, creatinine 1.0 mg. per cent, total cholesterol 283 mg. per cent, and cholesterol esters 206 mg. per cent. The serum contained 3.7 gm. of globulin and 3.3 gm. of albumin per 100 cc.

Withdrawal of ACTH was begun. Sutures sloughed from both biopsy wounds and healing was slow. By the twentieth day her lymphadenopathy and muscle tenderness were gone and she was able to walk. However, muscular weakness was extreme, and syncope due to postural hypotension occurred on several occasions. During the fourth week in the hospital painful erythematous stomatitis developed which cleared with local measures.

On the twenty-seventh day creatine excretion reached the remarkable level of 1,680 mg. in twenty-four hours. Review of the second biopsy by the Armed Forces Institute of Pathology was reported to show: "changes in the epidermis which tend to be psoriasiform but are not diagnostic of this entity. The changes in the muscle are those of an increased number of sarcolemma nuclei and slight degeneration of the muscle fiber."

Bilateral acute otitis media with fever (103°F.) developed on the thirtieth day. This responded to terramycin.® About the thirty-fifth day striking subsidence of the exfoliation was noted. Despite the encouraging progress of her skin lesions the patient remained depressed. Throughout her illness she had been rather mute and required much reassurance and cajoling to get her to eat, to resume walking and to try to help herself. On the thirty-ninth day she abruptly became violently agitated, with delusions and paranoid traits. She was transferred to a Neuropsychiatric Hospital.

She returned to us for follow-up examination seven months later, nine months after the onset of her illness. Her psychosis had cleared after withdrawal of ACTH and a long course of electroshock and insulin shock therapy. All of her muscular pain, tenderness and weakness were gone, she had regained her normal weight and felt entirely well. A complete blood count and urinalysis were normal. Urinary excretion of creatine was 168 mg. in twenty-four hours.

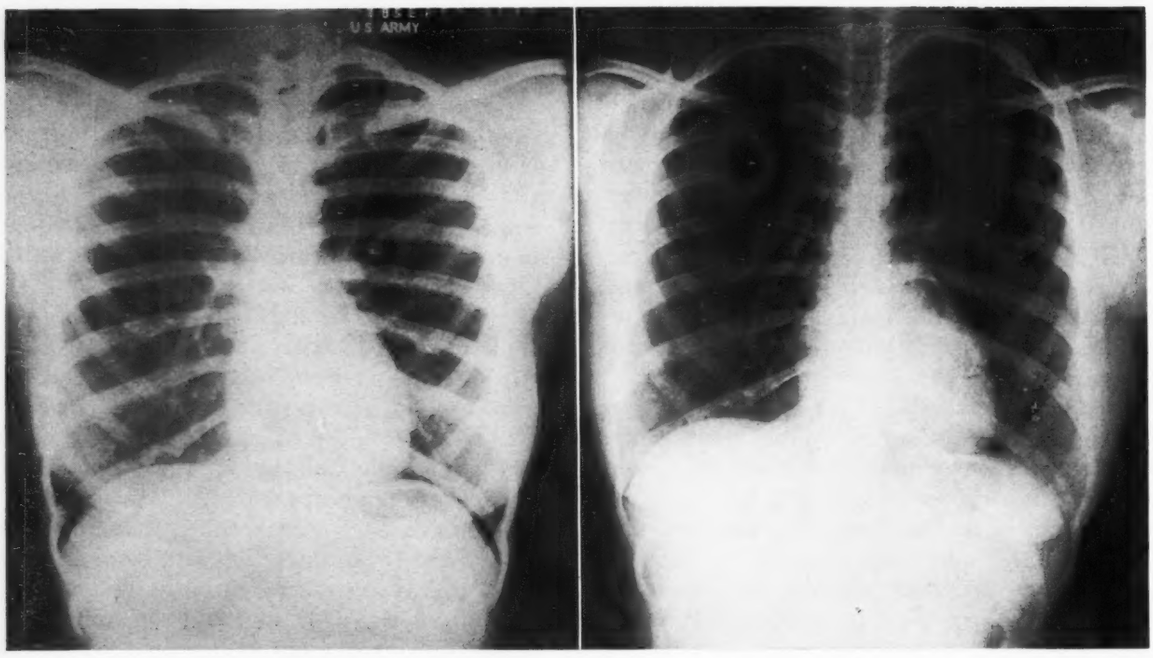
Although myositis and creatinuria are no longer in evidence at the time of writing, her present state probably represents remission rather than recovery since she still has moderate exfoliation involving the hands and feet, and serial chest roentgenograms show an increase of 1.5 cm. in the transverse diameter of the heart. (Figs. 5 and 6.)

The classic triad of polymyositis, edema and dermatitis was so striking in this patient that a firm diagnosis of dermatomyositis was possible in the face of negative biopsy reports. The intense creatinuria did much to bolster the diagnosis. Eventually a biopsy report consistent with the diagnosis of dermatomyositis was obtained.

Despite the fact that the microscopic changes described were consistent with dermatomyositis, this diagnosis was not ventured by the pathologists who reviewed the biopsies. This underlines an important point: the microscopic findings in dermatomyositis are non-specific and occur in several diseases. At best, when the microscopic changes are well advanced, as they were in the biopsy from our first patient, a pathologic diagnosis of dermatomyositis may be advanced, but not without hesitation. Furthermore, the chances of sampling a histologically involved site even in unquestionable dermatomyositis are far from 100 per cent. In short, a positive biopsy however desirable is not a *sine qua non*.

Psoriatic dermatitis[10] and exfoliative dermatitis[2] may occur in dermatomyositis but the combination of both in a single patient has not previously been reported. Stomatitis of the type presented by this patient occurs in approximately one-third of patients with dermatomyositis.[3,11] The spontaneous disruption and delayed healing of both biopsy wounds was disconcerting, and may have been related to ACTH therapy. Wound disruption (laparotomy) was noted by Cottell[12] in a patient with dermatomyositis who was not under treatment with ACTH.

Electrocardiograms and fluoroscopy gave evidence of cardiac involvement but were not specific enough to permit a definite diagnosis of either pericarditis or myocarditis. Enlargement of the cardiac silhouette on follow-up chest roentgenogram nine months after onset of her illness was additional evidence of cardiac involvement. Electrocardiographic abnormalities are frequent in dermatomyositis but pericarditis is rare.



5 6

FIG. 5. Case II. Chest roentgenogram, first month of illness. Normal cardiac silhouette.

FIG. 6. Case II. Ten months after onset. Increase of 1.5 cm. in transverse diameter of heart. Multiple films demonstrated persistence of the enlargement in all phases of respiration and during the Valsalva maneuver. Normal cardiac pulsations on fluoroscopy and a normal electrocardiogram suggest that this represents the effects of myocardial rather than pericardial involvement.

As with our first patient, a major complication necessitated the discontinuation of steroid therapy. Although her psychosis may have been precipitated by ACTH, it may actually have been an expression of dermatomyositic cerebral involvement since distinct pathologic lesions, involving particularly the frontal lobes, have been described in patients with dermatomyositis.[13]

REVIEW OF THE LITERATURE

Because our cases presented many unusual features it seemed desirable to determine the outer limits of the syndrome of dermatomyositis. It is evident from a review of the literature that while the fundamentals of dermatomyositis are polymyositis with creatinuria, dermatitis and edema, this disease is as protean in its manifestations as any other collagen disease.

Dermatitis. The dermatitis in dermatomyositis varies almost beyond belief. It may be erythematous, erysipeloid,[14] macular, papular,[4] telangiectatic,[15] purpuric, vesicular, bullous,[16] ulcerative, exfoliative[2,17] or psoriatic.[10,18] The skin may be shiny or dull, thickened or atrophic,[19] scaly or like wrinkled parchment. The accessory skin structures are often involved: hypertrichosis[19,20] and alopecia,[8,19,21,22] either patchy or diffuse, have been described. Hyperhidrosis,[22] photosensitivity[13] and Raynaud's phenomenon[11,21] may occur. Pigmentation, localized or generalized, may occur alone or with areas of depigmentation in the same patient.[13,19] Follicular keratosis[23] and pitting of the fingernails[18] have been mentioned. Dermographia,[19] urticaria,[19] erythema nodosum[24] and erythema multiforme[13] have called attention to the role of allergy in some cases. Subcutaneous calcification,[25,26] especially over pressure points, occurs almost as often in dermatomyositis as it does in scleroderma. On the other hand, skin changes may remain persistently absent.[11,12]

Edema. Facial edema, especially periorbital,[13] combined with cutaneous telangiectasia is very common in dermatomyositis and has given rise to the popular terms "heliotrope eyelids" and "heliotropic bloating."[14] Swelling may be confined to areas overlying inflamed muscle or may be generalized, tending to become dependent in ambulatory patients. It apparently bears little or no relation to the serum protein changes.[13] Although edema may involve the entire body surface, both intra- and subcutaneously, fluid

collections in the serous cavities are unusual[13] in dermatomyositis.

Myositis. Dermatomyositis can be diagnosed without dermatitis but not without myositis. The term "primary polymyositis" applied to this disease by earlier writers[11] served to emphasize the basic position of the muscular component in this syndrome.

The process may begin in any muscle, and remain limited to one muscle, but it usually involves many muscles in a bilaterally symmetric fashion, with a predilection for the neck,[27] shoulder and pelvic girdle.[28] Pain, weakness and stiffness are the presenting symptoms. Examination may reveal nothing abnormal, or may disclose muscles which are exquisitely tender,[29,30] swollen and doughy. As the disease progresses the muscles may become hard and fibrotic. Lumpy infiltrations and calcium deposits[22] may become palpable.

The tempo of muscle destruction varies greatly. The muscles may be so painful and tender as to make the patient cry out with the least motion or lightest touch. In other instances progressive weakness is the only sign of the insidious atrophy going on. Whether fulminating or gradual, severe loss of muscle tissue results in contractures and deformity[31] reminiscent of that following poliomyelitis. In severe cases the muscles of respiration and deglutition are involved, with death resulting from asphyxia or aspiration pneumonia. Extraocular muscle involvement has been reported.[27] Smooth muscle is never involved but significant myocardial involvement is not unusual.[9,11,13,18,19]

Creatinuria. Ever since Steinitz and Steinfield first recorded creatinuria in a case of dermatomyositis in 1931[30] many investigators have shown that urinary excretion of creatine is consistently and sometimes spectacularly[22] elevated in this disease. It is the most easily measured index of muscle destruction and is thereby the most helpful single laboratory test in the diagnosis of dermatomyositis. The creatine tolerance test (normals retain from 70 to 80 per cent of an oral dose of 1.32 gm. of creatine hydrate),[32] and quantitative analysis of muscle for creatine (normally 400 mg. of creatine per 100 gm. of muscle, decreased to about 200 mg. in muscle of patients with dermatomyositis) afford similar information but are beyond the reach of the average clinical laboratory.

Normal adult men excrete no creatine (up to 200 mg. per twenty-four hours in some laboratories) while women, children, castrates and elderly men may excrete amounts up to 400 mg. per twenty-four hours. Creatine excretion is unaffected by the menstrual cycle,[33] confinement to bed,[34] or by variations normally encountered in the average diet. Increase in the excretion of creatine may be reflected in a corresponding decrease in urinary excretion of creatinine (normally 1 to 2 gm. per day). Some authors attach special significance to the creatinine coefficient[35] (mg. of creatinine excreted in twenty-four hours/kg. body weight, normally 18 to 32; usually much less than 18 mg./kg. body weight in dermatomyositis).

Creatinuria in dermatomyositis may be intense, ranging in various reports as high as 1,100 mg. per twenty-four hours.[11] Creatinuria may also occur in other conditions. Those commonly listed include:[36] (1) Myopathies: muscular dystrophy, the myopathy secondary to amyotrophic lateral sclerosis, myotonia atrophica, amyotonia congenita. (2) Endocrinopathies: diabetes mellitus, thyrotoxicosis, acromegaly, Cushing's syndrome, Addison's disease. (3) Infection: poliomyelitis. (4) Diet: starvation. (5) Drugs: thyroid, ACTH, cortisone and epinephrine.

Scattered reports have mentioned[37] creatinuria in such various conditions as schizophrenia, tetany following parathyroidectomy, high fever of any origin, high protein diet, high carbohydrate diet, dinitrophenol ingestion, toxemia of pregnancy, malignancy, diseases of the liver and diseases of the heart. In these latter conditions creatinuria is rather poorly documented.

The differential diagnostic value of creatinuria in dermatomyositis is enhanced by the fact that creatine excretion is only slight in rheumatoid arthritis[38] and absent in fibrositis.[39] Significant creatinuria may occur in systemic lupus erythematosus,[40] a disease which at times is clinically difficult to distinguish from dermatomyositis. Here, however, the serum L.E. test provides differentiation.

Other Laboratory Findings. An elevated serum globulin is frequent in dermatomyositis. Moderate leukocytosis, 10,000 to 15,000 cells, is fairly frequent. Leukopenia and eosinophilia occur at some time in approximately one-fourth of cases. Anemia is absent or of the mild normochromic variety common to a great host of chronic inflammatory diseases. Elevation of the erythrocyte sedimentation rate is found in 25 per cent of cases.

The urine shows mild albuminuria, up to 2 plus, in about one-half of cases, and is otherwise negative except in very rare instances when severe renal involvement is present.[21]

Other abnormal findings described in isolated reports include low serum sodium, increased serum alkaline phosphatase, diabetic glucose tolerance test, decreased urinary excretion of 17-ketosteroids[40] and decreased peripheral utilization of glucose.[34]

Pathology. The histopathologic changes in the skin in dermatomyositis are not specific[13] enough to make the diagnosis. In the usual case with an erythematous rash, the microscopic findings consist of atrophy of the epidermis with thinning or loss of the dermal papillae, and edema of the basal cell layer with numerous "balloon cells."[41] The dermis and subcutaneous tissue show changes which clearly label the condition as a collagen disease. The collagen fibers undergo degenerative changes, i.e., homogenization, loss of staining ability and thickening.[2] The blood vessels show sclerotic changes in the collagen of their walls, hyaline subintimal proliferations[41] and perivascular cellular infiltrates. It should be noted that the cellular infiltrates in the subcutaneous tissue, around the blood vessels and, as will be noted later, in the muscles, are variable in their composition. The most common infiltrate is lymphocytic but polymorphonuclears, histiocytes and plasma cells are encountered, as well as occasional eosinophils and rare Langhans giant cells.

In the presence of the dermatitides which less commonly appear in the course of dermatomyositis, such as lichen planus,[19,25] eczema, poikiloderma, psoriasis and scleroderma-like patches, the microscopic findings merely mirror the clinical type of dermatitis which happens to be present.[11] However, the collagen and blood vessel alterations already described are basic and will persist to some degree.

The gross pathology of muscle involved by dermatomyositis is limited to abnormal pallor of the muscle and changes in consistency, either mushy or fibrotic and hard. Calcium plaques and hemorrhages are occasionally discernible. The histopathologic changes in muscle include acute degeneration of muscle, with a hyaline appearance due to loss of striations and altered affinity for stains, vacuolation of the cytoplasm, fragmentation and rupture of scattered fibers, blebbing of the sarcolemma sheath and increase in the number of sarcolemma nuclei.[19] The interstitial tissue regularly shows edema, scattered small hemorrhages and cellular infiltrates of varied composition, especially perivascularly. The lesions in cardiac muscle and in the muscles of the tongue and esophagus are identical though usually less profound than those in skeletal muscle.[9] As the disease advances muscle is replaced with fibrous tissue and the end stage is characterized by dense scarring.

Involvement of Other Organs. Although skin and muscle involvement are preeminent in dermatomyositis, this collagen disease like other members of the group may involve practically any organ in the body.

Mucous and serous membranes: Involvement of the conjunctiva[19] has been reported, and approximately one-third of all cases of dermatomyositis have stomatitis[3] the lesions of which include macules, punctate to diffuse erythema, hemorrhages, vesicles, ulcers, leukoplakic patches, pigmentary deposits, edema and scarring. Gingivitis and glossitis are usual accompaniments.

Serositis is unusual in dermatomyositis[42] but there are sporadic reports of pericardial effusion,[31] obliterative pericarditis,[31] pleurisy with effusion,[43] ascites and anasarca.

Cardiovascular system: Raynaud's phenomenon and acrocyanosis[11,21] are fairly frequent manifestations of the widespread arterial involvement in dermatomyositis. In one case differentiation from Buerger's disease was difficult.[44]

The high incidence (approximately 25 per cent) of cardiac involvement in dermatomyositis is perhaps not surprising in view of the fact that the myocardium is striated muscle. Tachycardia out of proportion to the degree of fever, systolic murmurs, pericardial friction rub and auricular fibrillation have been encountered. The most common electrocardiographic abnormalities are low voltage and evidence of nonspecific myocardial damage, both right and left hypertrophy and "strain" having been reported. At autopsy cardiac enlargement and histologic evidence of myocarditis have been repeatedly verified.[9,18,45] Aschoff's nodules are consistently absent.[22]

Respiratory tract: Dermatomyositic destruction of laryngeal and thoracic muscles may produce dysphonia, hoarseness, slowness of speech,[46] dyspnea and difficulty in coughing. Pulmonary infiltrates in dermatomyositis have been described as miliary,[25] hilar[19] and basal linear.[41]

Pathologic evidence as to the nature of these pulmonary lesions is lacking.

Gastrointestinal tract: Gastrointestinal ulceration with hemorrhage and perforation may occur as a result of intimal thickening and thrombosis of small submucosal arteries, anywhere from the esophagus to the rectum.[9] Involvement of striated muscle in the esophagus may cause dysphagia and external anal sphincter may produce fecal incontinence.[46]

Genitourinary tract: Gross hematuria, azotemia[47] and hypertension[42] occur, although rarely, in dermatomyositis.

Central nervous system: Cerebral lesions consisting of petechial hemorrhages,[48] perivascular and interstitial lymphocytic infiltrations,[49] neuronal damage and glial proliferation in the frontal lobes and cranial nerve nuclei[13] have been discovered at autopsy. Disorientation,[41] hallucinations and delirium[19] are encountered clinically. Paresthesias,[21] hypesthesia and lancinating pains have been described, and are attributable to perineural inflammation with demyelinization[13] which can be demonstrated in peripheral nerves. By far the most common "neurologic" abnormality in dermatomyositis, depressed to absent tendon reflexes, is not neurologic at all but simply a result of muscle degeneration and weakness.

Skeletal system: Stiffness and pain on motion, often the earliest symptoms in dermatomyositis, are easily misdiagnosed as arthritis but the incidence of true articular involvement in this disease is only about 5 per cent.[11] In an occasional case the joint process is indistinguishable from rheumatoid arthritis.[49,50] Pathologic study of the joints in dermatomyositis is nowhere to be found in the literature.

Bony involvement in dermatomyositis has been limited to osseous cysts and osteoporosis,[24,31] which may be acute. Milhorat et al.[51] reported decreased urinary excretion of calcium. Serum calcium values have been variously reported as low, normal and high.

Lymphatic system: Generalized lymphadenopathy and splenomegaly[19] have been reported in dermatomyositis. The splenic enlargement may be variable,[13] becoming more pronounced with exacerbations of the disease and receding during periods of quiescence.

Eyes: Diplopia may result when the polymyositis involves extraocular muscles.[27] Iritis occurs rarely[19] but retinopathy with hemorrhages, exudates and pallor of the discs has been detailed repeatedly, together with excellent pathologic studies of the involved eyes.[52]

DIFFERENTIAL DIAGNOSIS

Repeatedly listed in the differential diagnosis for dermatomyositis are such conditions as trichinosis, myasthenia gravis, myositis ossificans, erythema nodosum and Addison's disease. Today the diagnosis of these diseases is a relatively simple matter compared to the differentiation of dermatomyositis from other collagen diseases.

Some considerations of value in delimiting dermatomyositis from the other collagen diseases are as follows:

Systemic Lupus Erythematosus. The dermatitis in dermatomyositis and systemic L.E. is sometimes indistinguishable. Poikiloderma and erythema are the most common skin changes in each disease. In systemic L.E. the "butterfly rash" is said to be pathgnomonic, whereas in dermatomyositis the terms "heliotrope eyelids"[11] and "alabaster facies"[53] have similar import. The variety of dermatitis is much greater in dermatomyositis, in fact it is almost unlimited, ranging from total absence of skin changes to the most spectacular types (ecchymotic, bullous, exfoliative). In both L.E. and dermatomyositis there is depression of 17-ketosteroid excretion, and creatinuria.[40] In dermatomyositis, however, myositis with creatinuria is outstanding, whereas it is minimal in L.E.[54] The serum L.E. test has never been found positive in a case of dermatomyositis.[54] Polyserositis, arthritis, myocarditis and nephritis occur in both diseases but are decidedly more frequent and severe in systemic L.E.[55]

Scleroderma. Thickening and hyalinization of the subcutaneous connective tissue with atrophy of the overlying skin, a not uncommon combination in dermatomyositis, is responsible for the occasional misdiagnosis of scleroderma in patients with dermatomyositis. A few "burned out" cases of dermatomyositis have presented a final picture clinically indistinguishable from scleroderma. Moreover, Raynaud's phenomenon and subcutaneous calcification occur in both diseases. This confusion caused much debate and Osler was prompted to remark that "dermatomyositis is after all a deep seated scleroderma."[56] Distinction between the two diseases is now more clear cut: in dermatomyositis the cardinal characteristic is muscle involvement whereas scleroderma involves chiefly connective tissue, whether it be

subcutaneous, submucosal (esophagus and intestines) or interstitial (lungs and heart). Histologically, many patients with scleroderma show muscle involvement but it is the atrophy of disuse rather than the inflammation and subsequent destruction of muscle which is seen in dermatomyositis.[57]

Periarteritis Nodosa. The close relationship between periarteritis nodosa and dermatomyositis is most evident under the microscope. Perivascular infiltrates, hyalinization of the vascular collagen, intimal proliferation and thromboses of the small arteries occur in both diseases. Eosinophils may be increased in the blood and in the tissue cellular infiltrates in dermatomyositis to further the confusion, although seldom to the degree seen in periarteritis nodosa. Inflammation in the muscles may occur in periarteritis nodosa but it tends to be periarterial instead of the widespread muscle destruction characteristic of dermatomyositis. In periarteritis nodosa skin involvement is unusual. Nephritis, hypertension and neuropathy are common in periarteritis, insignificant in dermatomyositis.

Rheumatoid Arthritis. While involvement of the joints occurs in dermatomyositis, at times mimicking rheumatoid arthritis closely, more commonly there is juxta-articular pain, stiffness and tenderness due to muscular inflammation. Degenerative changes in muscle have been described in rheumatoid arthritis,[58] as has creatinuria. However, there are but faint shadows of the devastation which characterizes dermatomyositis.

ETIOLOGY

Speculation as to the cause of dermatomyositis has run the gamut from protozoal infestation to a dysfunction of the autonomic centers in the floor of the fourth ventricle. Suffice it to say that no single agent has been consistently incriminated and there is reason to believe that dermatomyositis is a syndrome which has diverse causes.

O'Leary and Waisman[11] cultured streptococci and staphylococci from ten of seventeen muscle biopsies and obtained clinical improvement with the use of autogenous vaccines in some cases. Dermatomyositis has appeared so often in patients with tuberculosis[21,30] as to suggest a cause and effect relationship.

In recent years attention has been focused on the remarkable incidence of carcinoma in patients with dermatomyositis. Carcinoma developed in eight of forty-five patients with dermatomyositis (18 per cent), according to Curtis et al.[59] These authors collected twenty-seven similar cases from the literature and we found sixteen additional cases[12,22,26,27,46,60,61,62] reported since their article was published, for a total of fifty-one such "coincidences." No particular type of cancer is incriminated, those reported include (in order of frequency): neoplasm of the ovaries, breast, reticulo-endothelial system, stomach, gallbladder, cervix, rectum, esophagus, lung, kidney, pituitary, parotid, bone and retroperitoneum. Of special interest is the improvement in the dermatomyositis which has been observed to follow treatment of the neoplasm, whether by irradiation or surgery.

Although the exact relationship of cancer to dermatomyositis is not clear, the hypothesis has been offered that dermatomyositis may arise on the basis of an allergic reaction to protein breakdown products of the tumor. There is also increasing support for the view that in patients with dermatomyositis sensitization to a variety of antigens such as the tubercle bacillus, streptococci or their products, may be the basic pathogenetic mechanism. This is in line with the current concept that the etiologic common denominator in the collagen diseases is the vascular "hypersensitivity" reaction described by Rich.[63]

PROGNOSIS

Dermatomyositis is a more severe disease with a higher mortality during the first few decades of life when muscular development and activity are at a high level. Fulminating cases with death in six to eight weeks are rare, occurring only in children, the usual case running its course in an average of two years.[30] The over-all mortality rate is 50 per cent with considerable morbidity among the survivors in the form of fibrotic muscular atrophy. Spontaneous remissions may last as long as eight years,[11] which makes evaluation of treatment uncertain. The most common cause of death is aspiration pneumonia initiated by weakness of the muscles of deglutition and respiration. Fatal termination may also be produced by myocarditis, intestinal perforation and uremia.

TREATMENT

ACTH and cortisone abolish the inflammatory manifestations of dermatomyositis (fever,

tachycardia, erythema, leukocytosis and elevated erythrocyte sedimentation rate)[64] but this is a non-specific effect, even though it may be of enormous temporary benefit to a prostrated "toxic" patient. More specific improvement has been reported, i.e., reduction of creatine excretion,[65] increase in muscular strength and conversion of muscle biopsy to normal.[66] Prolonged remissions have been induced with steroid therapy but in some patients relapse promptly follows withdrawal of the hormones.[67]

Reduction in creatine excretion and a return toward normal of muscle consistency to palpation and of muscle strength in patients with dermatomyositis have been reported to follow the use of wheat germ oil and tocopherols.[23]

The protein anabolic action of testosterone has led to the trial of this hormone in dermatomyositis, a muscle-wasting disease. Sustained remissions have followed its use[68] but evidence of its value cannot be classified as more than a clinical impression. Thorn et al.[69] recommend the use of testosterone to maintain control of dermatomyositis once a remission has been induced with ACTH and cortisone.

SUMMARY

Two cases of dermatomyositis are described. One patient had severe muscle atrophy, arthritis with contractures, dependent edema and pleuropulmonary involvement. Dermatitis remained absent. The second patient presented psoriasiform dermatitis which became exfoliative, generalized edema and evidence of cardiac involvement.

Striking creatinuria was present in both patients and its diagnostic value is emphasized.

Gastric ulcers with hematemesis developed in one patient and acute psychosis in another, complications which may have been due either to ACTH-cortisone therapy or to dermatomyositic involvement of the stomach and brain, respectively.

A review of the literature reveals that dermatomyositis has protean manifestations but can nonetheless be clinically differentiated from the other collagen diseases. To date fifty-one instances of carcinoma and dermatomyositis occurring in the same patient have been reported. It has been suggested that the incidence of carcinoma in these patients is more than coincidental, and that search for an occult neoplasm is indicated in every patient with dermatomyositis.

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Whipple's Disease*

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IN 1907 G. H. Whipple[28] wrote of "a hitherto undescribed disease characterized anatomically by deposits of fat and fatty acids in the intestinal tissue and mesenteric lymphatic vessels" and characterized clinically "by gradual loss of weight and strength, stools consisting chiefly of fat and fatty acids, indefinite abdominal signs and a peculiar multiple arthritis." He described the large pale macrophages which gave a negative reaction to fat stains and told of the polyserositis. Thus he recorded all of the outstanding characteristics of the entity which bears his name.

Sixteen years elapsed before the next reported case,[3] and a total of only six cases had been reported by 1931. With increasing awareness of this entity by clinician, surgeon and pathologist, fifty-three cases have been reported since 1931, and diagnosis by laparotomy and biopsy, first recorded in 1947,[18] has now become the rule. Ante mortem diagnosis has resulted in additional investigation and treatment, and recent results of treatment with ACTH and cortisone[7,13,23,24] have been encouraging in this otherwise fatal condition.

Because of the prominent lipid collections in the intestinal mucosa and mesenteric lymph nodes, the terms "lipogranulomatosis" and "intestinal lipodystrophy" have become ingrained in the literature. Although anatomically descriptive, the etiologic implications of these terms seem to be in error. The most characteristic elements of the lesion are the collections of sudan-negative macrophages in the lymph nodes and in the tunica propria of the mucosa of the small bowel. Black-Schaffer[2] demonstrated that the material within these cells reacted positively to the periodic acid Schiff test, and his studies led him to the conclusion that this material was a glycoprotein. Histochemical studies made by Upton[25] resulted in the same conclusion. Of further interest in this regard was the demonstration of an abnormal amount of glycoprotein in the serum of the one patient tested.[24] Although of help in reorienting etiologic concepts, these observations have not resulted in establishment of the fundamental etiology. The arthritis and polyserositis, the course and variability of the illness, the occasional occurrence of endocarditis and vascular lesions and more recently the beneficial results of ACTH and/or adrenocorticosteroid therapy have all brought support to Clemmesen's suggestion[5] that this is another entity in the group of "rheumatic" or "collagen system" disorders. Aschoff bodies[12] and "wire-loop" deformities[20] have each been demonstrated in patients with this disease on one occasion. In investigating this relationship further Jones et al.[13] were not able to demonstrate any PAS-positive material in the cells of the small intestines of a few patients with scleroderma, rheumatoid arthritis or disseminated lupus erythematosus. Other observers have suggested that faulty absorption of abnormal mucin (possibly produced by the intestinal mucosa) results in a generalized allergic reaction as well as phagocytosis of the material by the regional reticuloendothelial cells.[2,25] The latter proposal has the advantage of "explaining" the most distinctive element of the disorder, its distribution, and the systemic features of the disease.

To date, a total of fifty-nine cases[1,4,8,10,15,22–24,26] have been reported as Whipple's disease. Some of these diagnoses have been in error. At present, the only safe criterion for diagnosis would appear to be the characteristic PAS-positive macrophage in the typical distribution, regardless of other findings.

The authors wish to record four more instances of this entity to emphasize the diagnostic value of peripheral node involvement, to report the occurrence of the disorder in siblings and to comment on the possible role of genetics in the etiology. No attempt will be made to give complete anatomic descriptions of the lesions but enough data will be given to document the cases.

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CASE REPORTS

CASE 1. C. S., a forty-three year old, white, single, Canadian man employed as a chrome plater, was first seen at The Henry Ford Hospital in September, 1943. The chief complaints were of abdominal cramps and diarrhea of three weeks' duration. The patient considered his previous general condition to have been good. He had had migratory polyarthritis of unstated duration which had cleared prior to the onset of diarrhea. He denied any venereal disease. The right ankle had been fractured in 1928. He suffered from urticaria "when overheated." He had used alcohol freely until five weeks prior to admission. He had a mild chronic cough, suffered frequent "colds" and had occasional "hemoptysis," the latter being attributed to the acid used at his place of employment. He had also had frequent night sweats.

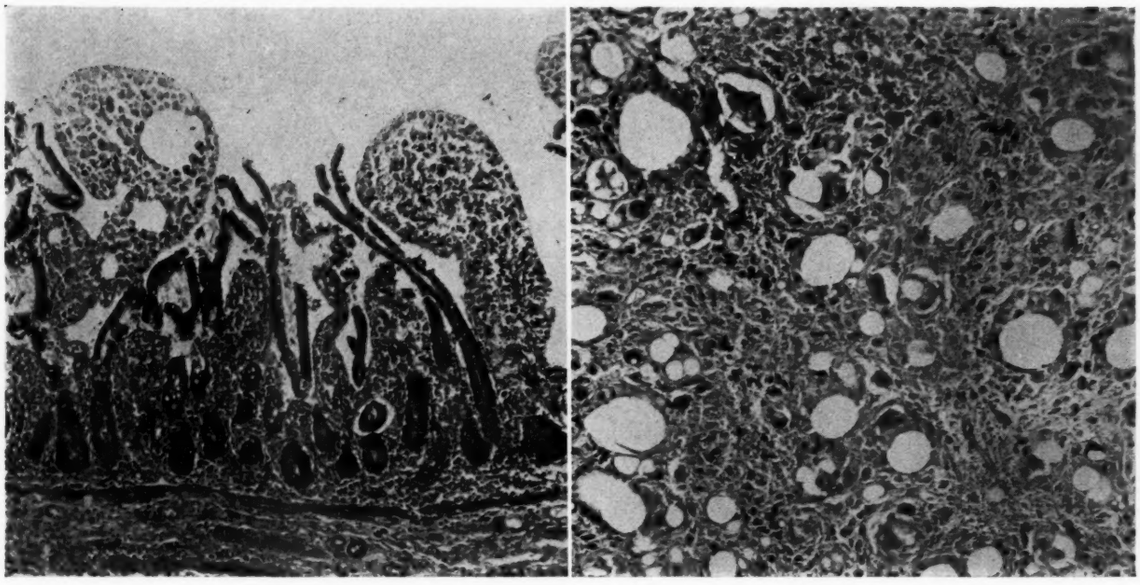
With the present illness the patient had lost 18 pounds. He had experienced nausea, occasional vomiting and attacks of generalized abdominal cramps. He had numerous watery, tan, malodorous bowel movements without mucus or pus, but some blood had been noted during the previous four days. Appetite remained good. Vomiting occurred three to four hours after meals and followed generalized abdominal cramps. The vomiting was unrelated to fatty food intake.

Physical examination revealed a thin, well developed, white man in no apparent distress. His temperature was 98.6°F., pulse 80, respiration 20 and blood pressure 110/68. There were upper and lower partial dental plates. "Pyorrhea" was marked and oral hygiene was poor. No abnormal pigmentation was noted. Cardiac examination gave normal results except for soft apical and basal systolic murmurs. A herniorrhaphy scar was present in the right inguinal region, and slight inguinal adenopathy was present bilaterally. Abdominal, neurologic, genital, rectal and musculoskeletal examinations gave normal results.

Proctoscopic examination revealed ulcers from pinpoint to 1 mm. in diameter throughout the examined region; surrounding mucosa was normal. Several weeks later this was not present. Hemoglobin was 7.4 gm. per cent, white blood count 15,300 mm.^{3}, urine specific gravity 1.032 and otherwise normal. Kline exclusion and cephalin-cholesterol tests gave negative results. Examination further revealed normal fasting free HCl and normal response to histamine on gastric analysis, normal duodenal drainage except that enzymatic studies were not done and a barium enema gave normal results. Fluoroscopically the gastrointestinal series showed spasm of the antrum and a possible ulcerating lesion on the lesser curvature of the stomach that was not demonstrated on the films.

Discharged on an ulcer regimen, the patient returned ten days later with severe abdominal cramps and distention. Abdominal x-ray showed considerable gas in the large bowel. Symptoms now included pain in the back immediately after meals. The patient's temperature was 99.2°F. and pulse 80/min. Additional observations included a distended tympanitic abdomen with moderate generalized tenderness and lymphadenopathy in the supraclavicular, axillary and inguinal regions. Hemoglobin was 7.7 gm. per cent, red blood count 3.5 M/mm.^{3}, white blood count 11,300/mm.^{3}, neutrophils 78 per cent, lymphocytes 19 per cent and eosinophils 3 per cent. Urine was normal except for 22.5 mg. of albumin/100 cc. He developed a daily afternoon fever which reached a maximum of 102°F. every fifth day. White blood cells ranged from 11,300 to 17,840/mm.^{3} with differential ranges of neutrophils 78 to 87 per cent, lymphocytes 9 to 19 per cent and eosinophils 1 to 4 per cent. An axillary node biopsy and later, a laparotomy were undertaken, the latter revealing considerable clear fluid in the abdomen; the mesenteric lymph nodes were found to be greatly enlarged and rather firm. One of these was removed. The total protein of the abdominal fluid was 1.5 gm. per cent. Plasma protein at this time was 3.9 gm. per cent. Following surgery the patient symptomatically improved and was afebrile for eight days. He received x-ray therapy, thereafter developed severe nausea, returned to his previous febrile pattern which progressed to daily spikes to 103°F. and again developed diarrhea with rapidly progressive inanition. Without the slightest response to therapy the patient died on the fifty-fifth postoperative day.

Autopsy revealed the body to be undernourished and there were numerous petechial hemorrhages in the skin. Both the left portion of the pleural cavity and the pericardial sac were obliterated by dense fibrous adhesions. Moderate pulmonary edema and pneumonia was present. The main findings were in the



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FIG. 1. Case I (C. S.), section from jejunum; villi show clubbing due to accumulation of PAS-positive macrophages; hematoxylin and eosin stain.

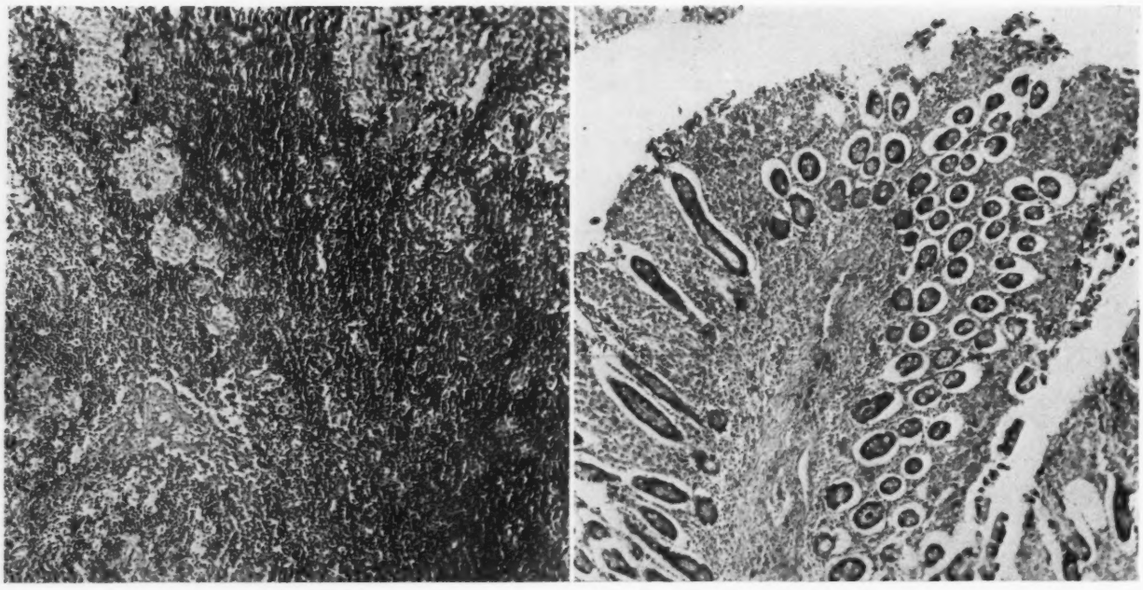
FIG. 2. Case I (C. S.), section from mesenteric node; black cells represent PAS-positive macrophages. Note fat vacuoles surrounded, in many instances, by foam cells and giant cells; periodic acid Schiff stain.

abdomen. It contained about four liters of clear yellow fluid, and the mesentery of the small bowel was thickened and attached to the retroperitoneal mass. The mass was composed of enlarged lymph nodes which were yellow-orange, firm and honeycombed on cut section. The bowel showed only some thickening of the rugal folds. The liver was slightly enlarged with fibrous thickening of its capsule.

Study of the sections showed characteristic change. The small bowel had thickened villi due to accumulation of PAS-positive macrophages. (Fig. 1.) There was also edema and moderate infiltration of the submucosa with these macrophages. The mesenteric nodes also showed typical nests of PAS-staining macrophages and fat vacuoles eliciting a foreign body reaction. (Fig. 2.) In peripheral nodes the characteristic masses of PAS-positive cells were also present. (Fig. 3.) Retroperitoneal connective tissues in general contained numerous PAS-positive cells scattered diffusely. Nests were also seen in the portal areas in the liver.

CASE II. P. V., a twenty-seven year old married Lithuanian dairy farmer, was first admitted to the Henry Ford Hospital in October, 1944. The chief complaints were of "inflammatory rheumatism" of two to three years' duration and "epigastric pain" of one year's duration. At age sixteen he had had difficulty for two months in raising either arm to the horizontal position. This was diagnosed as "rheumatism" and cleared spontaneously. A bullet was excised from the mandible at age twenty. At age twenty-one he suffered "head and internal injuries" in an automobile accident and was disabled for nine months.

Two to three years prior to admission he had developed a polyarticular migratory joint disturbance with swelling, tenderness and pain. This had been quiescent for some months prior to hospitalization. For several years he had also been subject to mild attacks of cramping abdominal pain. During the preceding year these attacks had been much more severe. Initially the pain had been dull and aching, had been localized over the anterior lower portion of the chest and upper portion of the abdomen bilaterally, had radiated to the left shoulder and dorsal spine. These attacks usually occurred once every ten to fourteen days and lasted several days. The distress was aggravated by jarring, lifting, sneezing, coughing and particularly by deep respirations. Recent cramping in the upper portion of the abdomen had been severe and at its worst one-half hour after eating. There was mild, dull pain in both costovertebral angles with no associated urinary symptoms



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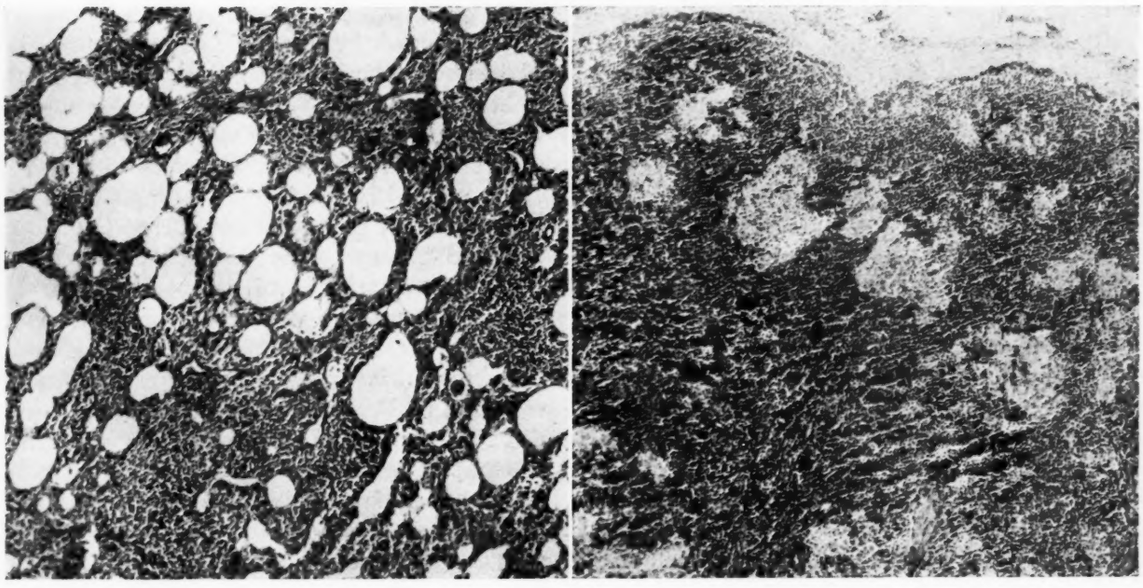
FIG. 3. Case I (C. S.), section from axillary node; numerous nests of macrophages in the cortex filled with PAS-positive material; hematoxylin and eosin stain.

FIG. 4. Case II (P. V.), section from jejunum; stroma of mucosa filled with plump macrophages; hematoxylin and eosin stain.

other than nocturia (one to two times) for the preceding four months. He was subject to slight shaking chills followed by slight fever and had lost 27 pounds in the preceeding six months. He drank unpasteurized milk and had had contact with "Bang's" disease. Tests for brucellosis previously had given negative results.

Physical examination revealed an asthenic, pale, thin youth who complained of abdominal pain. His temperature was 99.6°F., pulse 72/min., respiration 16/min. and blood pressure 100/60 mm. Hg. The skin was warm and moist and had a "grayish" appearance. The teeth contained many fillings. Lymphadenopathy was marked in the left axilla and "shotty" in the inguinal and cervical regions. The abdomen was tympanitic and "resistant," particularly on the left side. Pressure on a point of maximal tenderness located 4 cm. below and to the left of the umbilicus caused pain in the right costovertebral angle. Several examiners thought a mass was palpable in the left lower quadrant of the abdomen. The left testicle was slightly enlarged and there were small bilateral hydroceles. Motion of the back was restricted in all directions and there was tenderness on percussion over the lower dorsal portion of the spine.

Laboratory examinations revealed the hemoglobin to be 13.5 gm. per cent, red blood count 4.25 M/mm.^{3}, white blood count, 13,850/mm.^{3}, neutrophils 81 per cent, lymphocytes 13 per cent, eosinophils 6 per cent, sedimentation rate (Wintrobe) 6 mm./hour, serum non-protein nitrogen 33 mg. per cent, fasting blood sugar, 58 and 94 mg. per cent and serum diastase was normal. Repeated urinalysis revealed only a trace of albumin on one occasion and this specimen was negative for Bence-Jones protein; urine cultures gave negative results. Cystoscopic examination and intravenous and retrograde pyelograms were within normal limits. Biliary drainage (exclusive of enzyme studies) was normal. Fractional gastric analysis showed only two units of free HCl on the second specimen after histamine. Proctoscopic examination, gastric, colonic and small bowel x-ray studies after barium, and cholecystographic studies gave normal results. Slight thickening in the interlobar fissure on the right side was revealed by chest x-ray. X-rays of the spine were within normal limits. Blood cultures gave repeatedly negative results. Stools were consistently 3 to 4 plus guaiac-positive and on one occasion amebic cysts were seen. Agglutinations for Brucella abortus, typhoid, paratyphoid and dysentery, complement fixation and phagocytic index for Br. abortus, and skin test for brucellosis and trichinosis all gave negative



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FIG. 5. Case II (P. V.), section from mesenteric node; numerous fat vacuoles. PAS-positive macrophages are scattered through the stroma but are not easily seen; hematoxylin and eosin stain.

FIG. 6. Case III (E. V.), section from axillary node. Cortical nests of PAS-positive cells again well demonstrated; hematoxylin and eosin stain.

results. The Kline exclusion test gave negative results.

During hospitalization the patient ran an afternoon fever each day and this reached its maximum of 101°F. to 101.4°F. every five to six days. Abdominal pain and episodes of chills continued and he developed diarrhea. Hemoglobin dropped slowly to 10 gm. per cent, the white blood count remained around 9000/mm.^{3} with no significant change from the differential previously cited. Repeated sedimentation rates were always over 30 mm./hour.

Laparotomy revealed thickening of the wall of the small bowel, thickening and induration of the mesentery, and numerous firm, enlarged mesenteric lymph nodes, one of which was removed for microscopic examination.

The patient received x-ray therapy to the abdomen and supportive therapy. He was able to return home where he continued to be febrile, to have severe episodes of abdominal pain that would "double him up," and to have periodic chills, pleurisy and diarrhea. He refused to eat because this aggravated his distress, and continued to lose weight. Pigmentation increased. Diarrhea became profuse and terminally hemorrhagic. The patient died in another hospital two months later.

At autopsy, numerous hemorrhagic nodules were seen in the skin of the legs and in the intestine and kidneys. The mesenteric nodes were markedly enlarged and the cut surfaces were tan-orange.* Microscopic studies were limited to hematoxylin and eosin sections. The changes in the small bowel and in the mesenteric lymph nodes were again characteristic. They showed clubbing of the villi in the bowel due to large numbers of macrophages with abundant pale cytoplasm. (Fig. 4.) The mesenteric nodes showed both lipid accumulation and macrophages. (Fig. 5.)

CASE III. E. V., a thirty-five year old Lithuanian man employed as a factory worker, was admitted to the Henry Ford Hospital in August 1953. The chief complaints were of chills, fever, weight loss and diarrhea. A compound fracture of the tibia and fibula in the lower third portion of the right leg in 1939 had resulted in an unstable fibrous union which was repaired by bone graft in 1943. At this time there was a "branny macular type of eruption on the chest, back and buttocks." Blood pressure was 120/80 mm. Hg, hemoglobin 16.3 gm. per cent and other studies gave normal results. Eight months later a draining sinus developed. A generalized urticarial reaction followed a

* Data were obtained with the cooperation of Dr. G. W. Ramsey, Washington Hospital, Washington, Pa.

course of penicillin in beeswax. Sporadic treatment failed until healing was secured by saucerization and local streptomycin therapy in 1946. Hemoglobin was 13 gm. per cent, and other blood studies including erythrocyte sedimentation rate and urinalysis gave normal results at this time. The patient had gonococcal urethritis in 1946. In 1948 he developed a red papular pruritic lesion over the area previously described soon after beginning phenobarbital therapy, to which the rash was attributed. He also developed pretibial nodules. Both disappeared spontaneously without cessation of phenobarbital therapy. It was also in 1948 that the patient first developed a vague "hunger-type" abdominal pain localized in the periumbilical region which occurred sporadically and was unrelated to eating.

In 1951 the patient was admitted to the hospital because of painful, hot, swollen and tender joints of two and one-half years' duration. All of the larger joints had been involved at some time or another during this period. He had lost 20 pounds. The subject had had chilling sensations, attacks of pleurisy, a mild productive cough and night sweats. At this time abdominal distress was mainly postprandial. Examination revea'ed a tender, hot, swollen right ankle, tender nodes in the inguinal regions, "shotty" nodes in the axillae, and blood pressure of 105/60 mm. Hg.

Laboratory examination revealed the hemoglobin to be 12.3 gm. per cent, red blood count 4.11 M/mm.^{3}, neutrophils 63 per cent, lymphoyctes 30 per cent, eosinophils 7 per cent, non-protein nitrogen 38 mg. per cent, sedimentation rate 25 mm./hour (Wintrobe), serum uric acid 2.8 mg. per cent and urinalysis gave normal results. Electrocardiogram, intravenous pyelogram and retrograde pyelograms were within normal limits. Spine films revealed "fusion of the sacro-iliac joints indicative of an old Marie-Strümpell's arthritis." The patient received bile salts and salicylates at this time.

In 1952 a left epididymitis and orchitis developed which partially cleared during four weeks of aureomycin and sulfadiazine therapy only to recur on the right side. This too subsided. However, it was necessary to excise a non-painful, well circumscribed nodule ½ by 2 cm. in diameter from the anterior upper pole of the left testicle. Unfortunately, no tissue reached the laboratory. Cystoscopic examination and intravenous and retrograde pyelography were within normal limits. Reports of cultures and smears of the urine are not available. Film of the chest showed a small linear density on the right which was not thought to be significant. Blood studies at this time were not significantly different from those in 1951, except for a white cell count of 12,250/mm.^{3}

The patient gradually lost energy and initiative and became easily fatigued and irritable. Recurrent attacks of pleurisy, usually in the lower left anterior portion of the chest and radiating to the left shoulder, became more frequent and lasted three to seven days. Attacks of abdominal pain were more severe and were usually experienced in conjunction with chills, fever and profuse sweating. In addition to the aggravation caused by eating, there was a persistent dull generalized abdominal aching, and the subject was comfortable only when standing erect or when leaning far forward in the sitting position. He was also extremely uncomfortable for a short time after lying down. He became persistently nauseated but there was no vomiting, constipation, diarrhea or melena. All arthritis had subsided seven months before this admission in 1953.

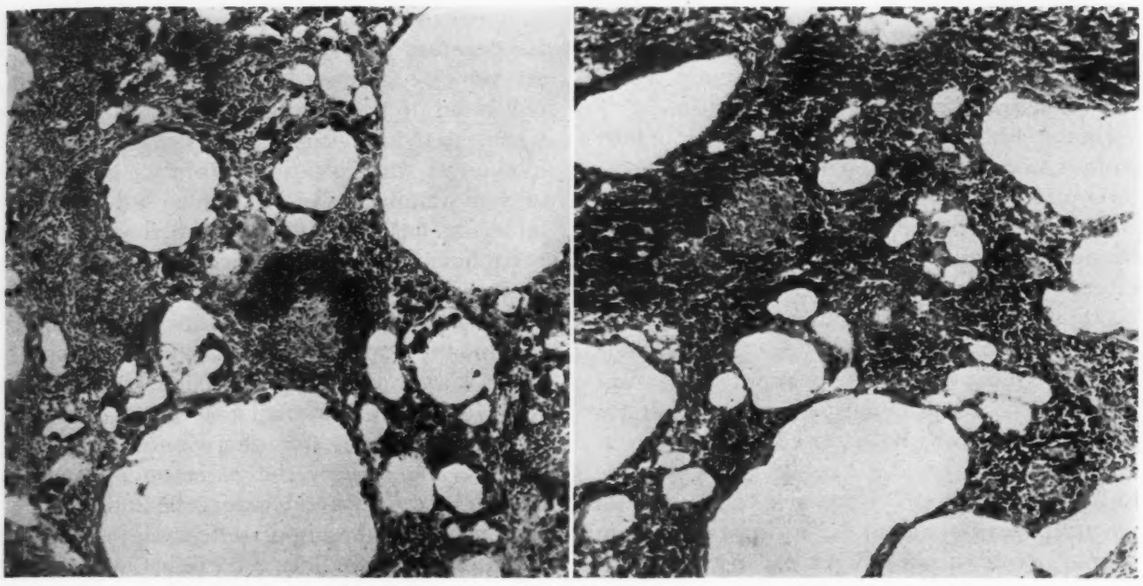
Physical examination revealed a chronically ill white man. His weight was 140 pounds, height 6 feet, temperature 99.4°F., pulse 76/minute and regular, respiration 20/minute and blood pressure 110/68 mm. Hg. His emaciation and general skin pigmentation were outstanding. The latter was particularly prominent over bony prominences and pressure areas but did not involve the oral mucosa. Lymphadenopathy consisted of small anterior and soft, flattened, pea-sized posterior cervical and supraclavicular nodes, several 2 by 1 cm. axillary nodes, and soft conglomerate nodes of the same size in the inguinal regions. He was edentulate. The abdomen had a "doughy" consistency. The liver was 4 cm. below the costal margin in the midclavicular line. In the left epigastrium there was a poorly defined tender mass descending on inspiration. The abdomen was hyperresonant except in the left hypochondrium. Peristalsis was decreased. There was three-plus rebound and localized tenderness at any abdominal area stimulated. Although there was a history of slight ankle edema and aphthous stomatitis, there was none at this time. A pleural friction rub was heard during an attack of pleurisy.

Laboratory examination revealed the hemoglobin to be 9.5 gm. per cent; red blood count

4.09 million/mm.^{3}; white blood count 20,000/mm.^{3}; differential, 90 per cent neutrophils, 7 per cent lymphocytes, and 3 per cent eosinophils; bone marrow myeloid/erythroid ratio 5.6/1 (normal 3/1 or 4/1) with 15 per cent eosinophils; serum non-protein nitrogen 35 mg. per cent; blood urea nitrogen 13 mg. per cent; creatinine 0.7 mg. per cent; uric acid 2 mg. per cent; albumin 4.4 gm. per cent; globulin 2.9 gm. per cent; Van den Bergh direct 1.0 mg. per cent and total 2.0 mg. per cent; thymol turbidity test 1 unit; cephalin and thymol flocculation tests negative results; diastase 69 per cent; prothrombin time 15 seconds or 80 per cent; cholesterol 241 mg. per cent with 48 per cent esters; serum glycoproteins 15.7 and 8.2 mg. per cent tyrosine per 100 cc. (normal 2.5 mg. per cent); sodium 139 mEq./L.; potassium 4.3 mEq./L.; calcium 9.8 mg. per cent; phosphorus 4.2 mg. per cent; CO_2, 23 mEq./L.; chloride 98 mEq./L.; alkaline phosphatase 2.2 Bodansky units; eight hour intravenous ACTH tests normal results on two occasions; total direct eosinophil counts 934, 576 and 1546; tests for cryoglobulinemia negative results; urine negative for Bence-Jones protein on three occasions; Coombs' test negative results on two occasions; heterophil agglutinations, cold agglutinations, Widal test, brucella agglutinations, complement fixations and phagocytic indices, Wassermann test, Weil-Felix test, and P. tularensis agglutinations all gave negative results. Skin tests including first and second strength purified protein derivative of tuberculin, the Frei test, and the histoplasmin test gave negative results. Urine cultures for acid-fast bacilli gave repeatedly negative results. The only free hydrochloric acid obtained by gastric analysis was on the third specimen after histamine. The results of the oral glucose tolerance were: fasting 85, 30 minutes 172, 90 minutes 129 and 150 minutes 120 mg. per cent. BSP test resulted in 4 per cent retention at 45 minutes and 3.5 per cent retention at 60 minutes after injection. A seventy-two hour stool specimen by dry weight contained 47.3 per cent fat. Barium enema, chest, skull and pelvic x-ray examinations gave normal results. Upper gastrointestinal x-ray examination revealed a "deficiency pattern" in the small bowel. An axillary and inguinal node were removed; the changes are more fully described later. Among other suggestions, the possibility of Whipple's disease was mentioned.

While in the hospital the patient ran an intermittent undulating febrile course, the highest temperature being reached every fifth to seventh day at about 101°F. There were shaking chills and drenching night sweats, most marked when the temperature was maximal. He refused food, was deteriorating rapidly, and death seemed imminent within days. A laparotomy under spinal anesthesia revealed a lusterless peritoneum and a large, rather firm, nodular tumor mass between the leaves of the mesentery and extending into the retroperitoneal space. Additional similar tissue was found along the lesser curvature of the stomach. Both tissues were biopsied. The small bowel wall was thick and edematous but not otherwise unusual.

Following surgery the patient made an uneventful recovery and was afebrile and relatively asymptomatic for about sixteen days when all symptoms and findings recurred. One hundred mg. of cortisone per day over a two-week period had little effect on the fever or symptoms. Within four days from the beginning of subcutaneous administration of 100 units per day of ACTH gel, he was afebrile and asymptomatic. Slight physical overexertion would result in the return of both within a few hours. On this therapy alone the hemoglobin rose rapidly to 13.5 gm. per cent. For more complete therapy, folic acid, parenteral vitamin B_{12} in massive doses, bile salts, emulsifying agents, pancreatin and multivitamins were then added. He gained weight to 170 pounds without edema or other evidence of hypercorticism. The blood pressure was consistently about 110/60 mm. Hg. After two months he began to have cycles of fever and had a recurrence of symptoms of gradually increasing severity. Pigmentation constantly increased. Dosage was gradually decreased and, except for a temporary episode of arthritis and erythema nodosum, the condition did not become worse except when less than 40 units a day was given. On 100 mg. of compound F per day, given orally, the subject again experienced a remission. Pigmentation decreased markedly and even the recent brown-black scar cleared almost completely. However, a profuse diarrhea developed which was then controlled by diet, oral streptomycin and a return to ACTH gel at 80 units per day. He continued to lose weight, a cough of increasing intensity developed and he became extremely weak despite all measures. Pneumonia of the right lower lobe developed three days prior to death and was followed by abscess formation. No specific organism could be



7 8

FIG. 7. Case III (E. V.), section from mesenteric node. In the lymphatic nodule in the center there is a nest of macrophages which gave negative results with Sudan stains but positive results for a PAS stain. Numerous fat laden cells can be visualized. Sudan III stain and hematoxylin and eosin stain.

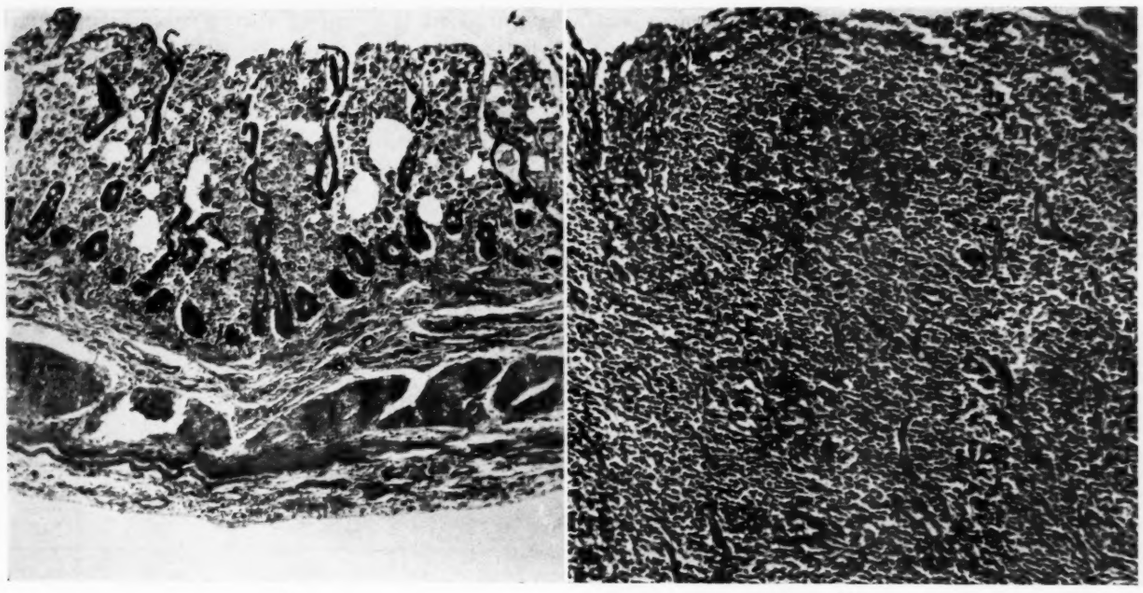
FIG. 8. Case III (E. V.), same as Figure 7 except for hematoxylin and eosin stain. The two types of macrophages may be difficult to distinguish without special stains.

identified and vigorous parenteral penicillin and streptomycin treatment was without effect. Temperature was sustained at 103 to 104°F. Platelet count and prothrombin time were within normal limits and hemoglobin was 12.5 gm. per cent the day prior to death. Acute shock developed one-half hour before death and did not respond to vasoconstrictor agents. The patient became comatose and died. Electrocardiograms the day before and twenty minutes prior to death showed inversion of T waves in leads V_3, V_4, V_5, but no evidence of electrolyte disturbance.

The cervical and inguinal nodes removed at surgery were moderately enlarged and pale. Study of the sections showed numerous nests of large pale macrophages scattered about, especially in the cortical portion. These showed fairly abundant pale cytoplasm and were PAS-positive. Germinal centers were small or absent. Some proliferation of reticuloendothelial cells and a mild amount of central fibrosis were present. (Fig. 6.) The axillary node showed a similar picture. Bacteriologic studies of material from these nodes failed to show specific organisms. The mesenteric node was enlarged, tan, firm and showed a fine honeycombing on cut surface. The section showed many characteristic nests of the PAS-positive macrophages plus many fat vacuoles. The latter were often surrounded by foam macrophages which were Sudan-positive. (Figs. 7 and 8.) Microscopic examination of the liver biopsy gave normal findings.

At autopsy the skin showed some increased pigmentation. About 200 cc. of slight turbid fluid were present in the abdomen and about 300 cc. in the right chest. The small bowel was distended with gas and injected. The mesentery was indurated and contained many enlarged tan, honeycombed lymph nodes. Dilated lymphatics were not seen. There was serositis of the liver and spleen and an adhesive pericarditis was present. Lobar pneumonia was present in the right lower lobe in the stage of gray hepatization. The mucosa of the small bowel was congested and several patches showed a granular pallor and a thickening of the plicae. The adrenals were small with atrophic cortices. Microscopic studies showed the characteristic macrophages in the mucosa of the small bowel (Fig. 9) and in the lymph nodes from mesentery and all peripheral areas.

Familial History of Cases P. V. and E. V. (Fig. 11.) The father of the patients in Cases II and III was living and in good health. No information was available as to the cause of death of the father's



9 10

FIG. 9. Case III (E. V.), section from jejunum. The PAS-positive macrophages in the stroma of the mucosa are well shown; hematoxylin and eosin stain.

FIG. 10. Case IV (W. McC.), section from axillary node. A large nest of PAS-positive cells can be observed near the periphery, as well as several other cells which are scattered; periodic acid Schiff stain.

parents. The remainder of his relatives were in good health with the exception of a nephew who had rheumatoid arthritis. The maternal grandfather was killed in an accident. The grandmother died at the age of sixty-three following a year's illness characterized by abdominal pain, diarrhea, emaciation and terminal hemorrhagic diarrhea. She is not known to have had arthritis.

According to the family there was no doubt that the patient's mother had died of the same disease as did the two sons. She had suffered for several years with a migratory polyarthritis characterized by hot, tender swollen joints which had been diagnosed as rheumatoid arthritis. With the onset of subsequent symptoms this disappeared. About one year prior to death she developed a prolonged upper respiratory infection. Hospital records state that she then began experiencing chills intermittently. On one occasion she had been suddenly seized with pain on deep breathing, chills, fever and marked perspiration, and had been hospitalized. She was an obese woman, was edentulate and febrile (102°F.) with a pulse of 120/minute and respirations of 40/minute. Numerous moist rales were heard on inspiration and expiration and a friction rub was heard on the right side posteriorly. No hemoptysis or congestive failure was evident. There were frequent extrasystoles. Studies revealed exaggeration of "parabronchial markings on the left" by chest x-ray, red blood count was 3.6 million/mm.^{3}, hemoglobin 71 per cent, white blood count 8.900/mm.^{3}, serum nonprotein nitrogen 27 mg. per cent and negative results were obtained from sputum cultures, acid-fast smears and serological tests for syphilis. On sulfadiazine therapy the temperature became normal after three days but then returned to 102°F. This temperature recurred several times during this twenty-day hospitalization. Following discharge she developed abdominal pain which later became severe and cramping in nature and was precipitated by eating. She developed increasingly severe diarrhea and meteorism. Weight loss was rapid. Eight months after the previous hospitalization studies revealed a trace of albumin by urinalysis, hemoglobin 51 per cent, red blood count 3.1 million/mm.^{3}, white blood count 5,500/mm.^{3}, neutrophils 74 per cent, lymphocytes 26 per cent and Kahn and Kline tests gave negative results. X-ray examination revealed a normal stomach and duodenum. Six hours after barium meal the small bowel was empty except for "a few scattered flecks," and the cecum somewhat conical in shape. Barium enema showed the cecum not adequately filled, the appendix was visualized and there was no reflux into the

terminal ileum; the remainder of the colon was normal. Postevacuation films were thought to show some increased density "apparently of soft tissue origin" over the right sacroiliac area. She became increasingly pigmented and emaciated. Terminally, the diarrhea became hemorrhagic and she died two and one-half months after the examinations described.

Of the mother's two siblings, a sister is living, has three children (two girls, one boy) and all are apparently well. The other, a brother, was institutionalized at the age of thirty-one following seven years of gradual mental deterioration during which time he was unable to support himself. He was apparently schizophrenic. At age thirty-two blood studies gave normal results except for slight leukocytosis. The serum non-protein nitrogen was 30 mg. per cent and chest x-rays each year were within normal limits until age thirty-five when slight cardiac enlargement was noted. A year later a right pleural effusion was noted. Two months later this had completely cleared. The red blood count was 3.7 million/mm.^{3}, hemoglobin 70 per cent, serum non-protein nitrogen 30 mg. per cent and fasting blood sugar 55 mg. per cent. Several urinalyses showed only numerous bacteria. Two months later enlargement at the hilum, thought to represent enlarged lymph nodes, was apparent. Some cardiac hypertrophy was still present. After another two months the serum non-protein nitrogen was 42 mg. per cent and chest x-ray showed interlobar effusion and effusion extending over "the entire periphery" of the left lung. Bilateral hilar enlargement remained. The sedimentation rate was 27 mm./hour. Sputums for acid-fast bacteria on three occasions gave negative results. The serum non-protein nitrogen rose to 60 mg. per cent. Within the week he expired at the age of thirty-seven. Reportedly death was due to "coronary occlusion and congestive heart failure." No autopsy was performed.

Our two patients, P. V. and E. V., have three other siblings. A sister, age thirty-eight, is asymptomatic and normal by physical examination; normal results were obtained from oral vitamin A and glucose tolerance tests. (Table 1.)

TABLE 1

Patient	Glucose Tolerance Test	Fasting		Six Hours After Oleum Percomorphum	
		Vit. A (μg. %)	Carotene (μg. %)	Vit. A (μg. %)	Carotene (μg. %)
E. V. (sister)	Normal	25.2	105	70	227
P. V. W. (sister)	Flat × 2 (rise 26 mg. %)	4.3	265	78	242
P. V. (daughter)	Normal	18.1	136	99	206
M. V. (daughter)	Normal	22.4	136	100	165

Another sister, age thirty-one, has had a two- to four-plus albuminuria persistently for at least eight years. At age eighteen there had been some pitting pretibial and ankle edema for about one month. For eight years there had been a chronic slightly productive cough, occasional asthmatic attacks, chronic fatigue, intermittent aching in the back of the legs, shoulder joints and under the left scapula, and intermittent abdominal cramps associated with gas. She has had temporal mandibular arthritis thought to be secondary to malocclusion. In 1947 there was a "toxic dermatitis" of the extensor surface of the forearms, shoulders and back. Physical examination revealed the subject to be normal except for a slight yellowish tint to the skin. The blood pressure was 118/78 mm. Hg. The twenty-four-hour urinary excretion of albumin was 5.1 gm. Hematologic studies, basal metabolic rates, stomach and small bowel x-ray studies, retrograde pyelograms and chest and joint x-rays gave normal results. The oral glucose tolerance curve was flattened and the fasting vitamin A level was 4.3 mg. per cent, the serum mucoproteins 2.8 mg. per cent, serum non-protein nitrogen 25 mg. per cent, albumin 4.2 and globulin 1.7 gm. per cent. The Kline exclusion test gave negative results. Stool fat content was within normal limits. There were no red cells and only an occasional cast in the

urine specimens. The urea clearance test shows 45 cc./minute standard and 54 cc./minute maximal clearance.

The remaining brother, age twenty-four, is a mongolian idiot and has been institutionalized since the age of eight. In 1943 he began to have white married factory worker, was first seen at the Henry Ford Hospital in December, 1953. He complained chiefly of intermittent looseness of the stools for four years. This condition had required hospitalization about twice yearly and usually ceased promptly with treatment. An

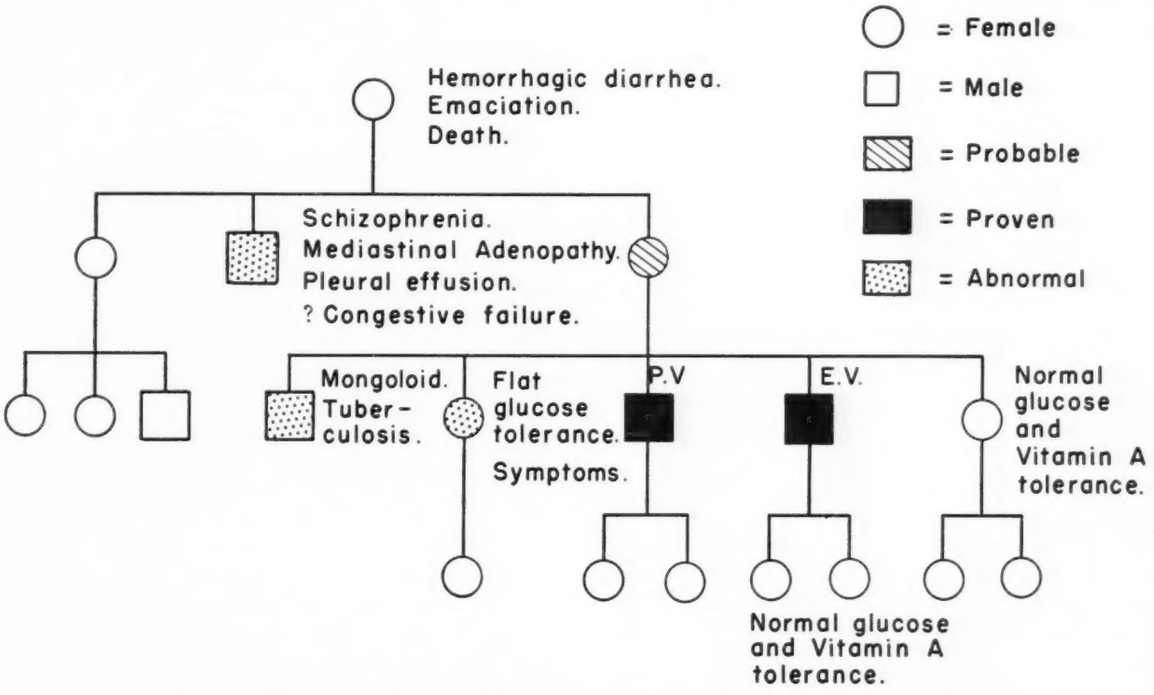


FIG. 11. Diagram of family history of patients P. V. and E. V. (Cases II and III).

temperature elevations, a rapid erythrocyte sedimentation rate and leukocytosis. Later in the year he developed bronchopneumonia in the mid-portion of the left lung. This cleared. In 1945 scarring at the apex of the right lung was noted. In 1950 the entire right lung and the upper two-thirds of the left lung showed small dense nodular shadows distributed evenly over the areas. Later there was a soft infiltrate noted in the apical areas and by 1953 x-ray examination revealed that the lesions had undergone considerable resolution although there was nodulation and fibrosis at both apices. It is assumed that he has tuberculosis although, due to lack of cooperation by the patient, this has not been bacteriologically confirmed. We have no information as to symptomatology or treatment received.

All seven children of the next generation are girls. The two children of patient E. V. gave normal reactions to vitamin A and oral glucose tolerance tests.

CASE IV. W. McC., a forty-nine year old attack lasted about five days with three to seven stools daily. Some upper abdominal distress occurred during attacks but no severe pain or cramps. There was never any constipation or any blood, pus or mucus in the stools. Anorexia occurred with the attacks and there was some difficulty with bloating and excessive gas during remission. The stools were light brown to cream in color, malodorous particularly at the time of diarrhea, and occasionally contained undigested food. Because of his complaints an exploratory laparotomy had been done three years previously and many enlarged mesenteric nodes had been noted. No biopsy had been done. The appendix was removed. Two years previously he had passed a right ureteral stone. On one occasion a paratyphoid organism was found in his stool. In 1953 cholecystectomy was performed and tissue from the mesentery was removed but a report of the tissue examination was not available to us. He had been anemic from the onset of his illness and had received transfusions totaling approximately 20 units on several occasions.

Following an attack of diarrhea and a temperature elevation to 101°F. he had received two units of blood two weeks prior to admission. Maximal weight had been 192 pounds ten years previously, and his normal weight over the last five years had been about 150 pounds. Weight upon admission was 135 pounds. For some time he had had mild night sweats and occasional edema in the left foot. He had been having nocturia three to four times, for ten years. Four years prior to admission he began to have migratory polyarthritis with painful, swollen joints, especially of the feet, knees and shoulders. He had had this intermittently until a year prior to admission. There had been an episode of jaundice at the age of twelve years.

The mother and father were living and were apparently in good health. A brother had died in 1931 after a two month illness which, according to the patient, was due to a ruptured appendix. No further details were available and a postmortem examination had not been done.

Physical examination revealed a well developed, thin, white man with generalized pallor. The skin showed a diffuse tan especially marked on the neck, the sides of the face, the forearms and the hands, and in the year-old cholecystectomy scar. He was edentulate. The blood pressure was 90/50 mm. Hg. The abdomen was hyperresonant throughout except in the left lower quadrant. There was deep paravertebral fullness and generalized abdominal resistance. A generalized perifolliculitis was noted and was most marked over the lower abdomen, thighs and lower legs and in a predominantly extensor distribution. In the latter areas there were perifollicular hemorrhages. This cleared rapidly following administration of a vitamin B and C preparation parenterally.

Studies showed the hemoglobin to be 9.2 gm. per cent, red blood count 3.59 to 3.79 million/mm.^{3}, cells hypochromic and microcytic by smear; white blood count 7,400/mm.^{3}, neutrophils 69 per cent to 77 per cent, eosinophils 1 per cent to 2 per cent, monocytes 0 per cent to 4 per cent; lymphocytes 19 per cent to 21 per cent; sedimentation rate 26 mm./hour (Wintrobe), hematocrit 32 per cent, serum nonprotein nitrogen 30 mg. per cent, cholesterol 98 mg. per cent, prothrombin time 14 seconds (90 per cent), albumin 4.1 and globulin 2.0 gm. per cent, serum amylase 75 per cent and lipase 78 per cent of normal; vitamin C level 0.20 mg. per cent; sodium 138 mEq./L., chloride 104 mEq./L.; calcium 9.2 mg. per cent, and phosphorus 3.4 mg. per cent. Urine examinations including cystoscopic examination, intravenous pyelograms and twenty-four-hour urine collections for acid-fast bacilli, gave normal results. The cephalin cholesterol flocculation, the thymol turbidity and flocculation, and the BSP tests gave normal results. Agglutinations for typhoid, paratyphoid and brucellosis, and the Kline exclusion test gave normal results. The stools were liquid, contained bile and occasional undigested meat fibers, but contained no ova or parasites. The twenty-four-hour stool specimen contained 48 per cent fat on a normal diet and 14 per cent fat on a restricted fat diet. The oral glucose tolerance test in mg. per cent was 85 at 0, 97 at 15, 129 at 30, 154 at 90, and 130 at 150 minutes. Stool cultures consistently gave negative results. Proctoscopic examination revealed no abnormalities. A gastric analysis revealed free acid in all fractions except the fasting specimen. By biliary drainage the lipase was 47 per cent, trypsin 26 per cent and the amylase 28 per cent of normal, and all bile fractions were within normal limits. Barium enema showed spasm in the sigmoid colon but the postevacuation pattern was within normal limits. Stomach and small bowel series revealed a probable small hiatus hernia and a definite deficiency pattern throughout the small bowel.

While in the hospital the patient had an elevated temperature to 99.6 or 99.8°F. about every fifth or sixth day but was otherwise afebrile. A peripheral lymph node biopsy was done. He was treated on a full sprue regimen but, although he gained about 6 pounds, his diarrhea recurred and small bowel x-rays showed no change in pattern. As the lymph node biopsy showed evidence of Whipple's disease, he was started on steroid therapy. Enough time has not elapsed for evaluation of the result.

The lymph node biopsy (Fig. 10) showed a moderate proliferation of the reticulo-endothelial cells. There were occasional clumps of macrophages, especially in cortical areas, and these were strongly PAS-positive.

CLINICAL ASPECTS

The diagnosis of Whipple's disease should be considered in every case which exhibits the features of sprue and which is preceded by a migratory polyarthritis. The arthritis is manifested by pain, swelling, tenderness and increased heat and is indistinguishable clinically

from rheumatoid arthritis. Although not usually accompanied by residual deformity, the x-ray findings are occasionally compatible with those found in Marie-Strümpell disease. Actually the arthritis is the commonest symptomatic manifestation of polyserositis which on anatomic examination is found to affect in decreasing frequency the pericardium, the pleura, the peritoneum and the endocardium. Lesions involving mesenteric and retinal vessels have also been described. The arthritis sometimes disappears during attacks of diarrhea and almost always has subsided by the time the patient is presented for care of the sprue-like manifestations of the disease. However, the polyserositis may still be active as evidenced by persistent attacks of pleurisy, pericarditis, peritoneal irritation, fever, elevated sedimentation rate and, in some cases, leukocytosis and eosinophilia. The complaints are usually of abdominal pain, diarrhea, asthenia and weight loss, and the findings are most consistently those of emaciation and hypotension and may include lymphadenopathy, pigmentation or fever. Any combination of the laboratory findings common to non-tropical or secondary sprue may be present but a microcytic anemia is the most constant phenomenon. Low serum protein is also frequently present. Small bowel dysfunction may be demonstrated by flat vitamin A tolerance test, x-ray deficiency pattern and often by a flat or delayed oral glucose tolerance curve. A doughy abdomen and/or an abdominal mass, usually on the left side, are helpful observations but apparently are not extremely common. To summarize, the over-all clinical picture is one which we would expect to see in the simultaneous occurrence of polyserositis and the malabsorption syndrome.

The clinical features of the disease can, however, be simulated by other entities and the only absolute diagnostic criterion at present is the typical microscopic findings in the small bowel and mesenteric lymph nodes. This includes the requirement that the macrophages be PAS-positive and essentially sudan-negative. Plummer et al.[22–23] have summarized the cases prior to 1953 and our references include all other cases reported to date.[1,4,8,10,15,24,26] As might be expected in a disease with such protean disturbances, cases have been published under the heading of Whipple's disease which, because of inadequate description of the lesions or because findings strongly suggest another entity, fail to satisfy this criterion. Ten cases have been indicted previously by others.[5,9,20] The case recently reported by Mendes[15] is characterized by atypical lesions; indeed, the diagnosis was rejected by reviewers of the material. Inguscio's case[10] completely lacks the study of tissue. However, we cannot agree with the opinion that the presence of chyloascites is reason to reject the diagnosis provided the other characteristic anatomic changes are present. There can be little doubt that lymph drainage eventually is blocked at the mesenteric nodes, that dilatation of the lymphatics takes place, and that eventually rupture and chyloascites could occur. Whether remission of the disease on non-specific therapy is reason to doubt the diagnosis cannot be stated emphatically. Certainly spontaneous remission and exacerbation is not uncommon in "rheumatic" disease or non-tropical sprue, the entities of which resemble this disease in many ways. It is similarly common to many diseases responding to cortisone and ACTH.

The disease is probably not as rare as the number of reported cases would seem to imply. Incognizance of the disease and the operative barrier to establishment of the diagnosis are probably the main factors responsible for the paucity of established cases. The material herein presented illustrates our own increasing awareness of the disorder, with diagnosis established twice by autopsy, the third time by laparotomy after the disease was suggested by peripheral node biopsy, and finally by peripheral node biopsy after the disease was suspected clinically. The latter means of diagnosis has obvious advantages and, because it avoids the hazards and expense of laparotomy and intestinal biopsy, can be undertaken more readily by patient and physician. This is apt to result in more frequent and earlier diagnosis. Since it is possible that the process is no longer reversible when in an advanced stage, which may account for the variable response to ACTH and corticosteroid therapy, early diagnosis may be of great importance.

Peripheral Node Diagnosis. Although peripheral lymphadenopathy is mentioned in about 50 per cent of the cases, few investigators have reported the results of microscopic examination. The presence of characteristic lesions in extra-abdominal nodes in this entity was first reported[14] in 1938. In 1952, in addition to reporting typical changes in the peripheral nodes, Upton[25] emphasized the wide distribution

of glycoprotein-containing macrophages in the periaortic and bronchial lymph nodes, in the periadrenal adipose tissue and in the liver. In the few remaining cases in which microscopic examination of peripheral nodes is mentioned it is stated that these nodes are not involved.

Our experience has shown that the diagnosis can be established with confidence by examination of peripheral nodes in these patients. All three patients in whom microscopic examination of peripheral nodes was done showed characteristic accumulations of Schiff-positive macrophages, especially in cortical areas. The changes are suggestive even in sections prepared by the routine hematoxylin-eosin technic. There is generally a moderate hyperplasia of reticulo-endothelial cells in the medullary sinusoids but in addition one can distinguish the unusual appearing nests of macrophages which are situated in the cortical areas. These nests are fairly discrete and are composed of cells which are slightly larger than the normal reticulum cells because of the accumulation of increased amounts of cytoplasm. The cytoplasm frequently shows fine vacuolization. In contrast to Upton's findings,[25] the lesions in our nodes showed no giant cell formation nor any similarity to a tubercle. Schiff stains disclose a marked reaction in these nests of macrophages and provide a pattern which we have not encountered in other processes.

In addition, our two autopsied cases confirmed completely the widespread nature of the distribution of the Schiff-positive material, as described by Upton.[25] Accumulations of macrophages were found in loose connective tissue of the retroperitoneal space and in focal accumulations in the liver. The generalized distribution of the material parallels the reticulo-endothelial system and suggests that phagocytosis by reticulo-endothelial cells is responsible for the material encountered in these areas.

Role of the Adrenal. The role of the adrenal gland in this disease is of interest and several observers[9,13,25] have reported the 17-ketosteroid excretion to be at the lower limits of or below normal. Adrenal hypocorticism would explain certain striking features of the disease, such as pigmentation, hypotension and asthenia. The emaciation, diarrhea and abdominal pain which are also usually present by the time the patient seeks treatment necessitate consideration of Addison's disease. Although it is possible that a relative adrenal insufficiency does exist, we believe adequate information is at hand to state that there is no intrinsic defect in the hypothalamic-pituitary-adrenal system.

The pretreatment 17-hydroxycorticoid excretion of patient E. V. was at the lower limits of normal. This was certainly not in keeping with the clinical impression of the severity of the stress. At that time the patient appeared critically ill. Twenty-five U.S.P. units of corticotropin administered intravenously over an eight-hour period resulted in an increase in 17-hydroxycorticoid excretion (Table II) and eosinopenia which were within normal limits. Marked symptomatic improvement followed and he remained afebrile for the next two days. Furthermore, long-term stimulation with corticotropin gel continued to produce high levels of 17-hydroxycorticoid excretion. Therefore, if relative adrenal hypocorticism does exist, it must result from failure of ACTH synthesis or release. Stress of the proper dimensions, however, produced an adequate adrenal response as suggested by temporary remissions precipitated by surgical intervention in two of our patients. This implies an intact ACTH-release mechanism. The eosinopenia in response to epinephrine, demonstrated by Jones et al. in

TABLE II

Date	Treatment	Dosage	Creatinine Excretion	17-hydroxysteroid Excretion (mg./24 hr. equiv. to Compound E)
9-12	None	.....	10.70	8.73
9-13	ACTH I.V. over 8 hr. period	25 U.	5.70*	14.1*
10-19	ACTH gel for 2 weeks	100 U each day	1,250	27.4
10-22	ACTH gel for 2 days; product of another company	100 U. each day	1,790	37.4
12-16	ACTH gel for 1 week	20 U. each day	1,208	15.1
2-13	Dihydrocorticosterone for 3 weeks	100 mg. each day	980	19
2-14	Dihydrocorticosterone	100 mg. each day	1,070	16.8
2-26	ACTH gel for 10 days	80 U. each day	780	26.1

* Denotes 8 hour collection period concurrent with administration of ACTH.

their patient, tends to support this assumption, although the validity of this test as a measure of pituitary-adrenal function is in doubt. The malabsorption state may lead to malnutrition with specific depletions which are adequate to account for the findings. Indeed, it seems extremely likely that the mechanisms producing these features in Whipple's disease are similar or identical to those operating in the malabsorption syndrome. In the latter condition no defect in the hypothalamic-pituitary-adrenal mechanism has been demonstrated to our knowledge, although a number of patients have benefited from corticotropin and corticosteroid therapy. These considerations and the failure of the induced adrenal hypercortical state to produce a universally favorable and sustained response in Whipple's disease make it unlikely that deficiency of adrenal corticoids plays any fundamental role in the etiology or fatal outcome of the disease.

Of further note was that the patient treated with corticosteroids seemed unusually resistant to the development of adrenal hypercorticism. On a 1 gm. salt diet with supplementary potassium there were no manifestations of hypercorticism despite a total of 2,400 mg. of cortisone, 7,000 mg. of hydrocortisone and 8,000 units of corticotropin gel in a six and one-half month period. Cortisone seemed to have no effect upon his illness. Hydrocortisone produced a temporary remission after an exacerbation during corticotropin therapy. As measured by urinary 17-hydroxycorticoid excretion, 20 physiologic units of corticotropin gel administered once daily, was essentially equivalent to 100 mg. of hydrocortisone per day. By the same measurement, 100 units of corticotropin gel daily produced twice the response of either of the foregoing. The poor response to cortisone when compared to corticotropin, reported by Plummer et al., may reflect not only differences in pharmacologic properties of the several corticoids but to some extent the inadequacy of the cortisone dosage.

Etiologic Considerations. A primary purpose of this report is to record the unusual familial occurrence of Whipple's disease. The condition described by Whipple has been considered a sporadically occurring entity of unknown cause, and most reports have neglected familial and environmental history. Hendrix and Black-Shaffer[9] emphasized that all their patients were long term residents of North Carolina. They considered the family histories of no significance in two cases; they did not record the family history in the remaining two. Whipple[28] reported that the family history was not contributory. Blumgart[3] found a family history of "gout" in his most acceptable case. The father of Gaertner's patient[7] suffered from rheumatism and heart failure. Paulley[19] noted that a sister of his patient had disseminated sclerosis. More recently, Story and Sagild[24] reported that their patient's sister suffered from diabetes and that two brothers and a daughter had died from cancer. In some ways this resembles the initial report we received concerning our patients' relatives. Gagne[8] mentions that other members of the family had cardiac troubles but does not specify further. Albertini's patient[1] suffered at the age of sixteen and twenty-two from a condition diagnosed as rheumatic fever. The remaining cases contain no definite statement concerning family history. No previous cases of familial occurrence of Whipple's disease are reported.

The family history in Cases II and III is presented in as much detail as is available so that the reader might make his own evaluation. The mode of death of the maternal grandmother is interesting but a definite conclusion as to the nature of her illness is impossible. The family regarded the illness preceding death of the mother at the age of forty-nine as identical with that of the brothers and emphasized the symptoms, time relationships and mode of death. Despite the fact that a carcinoma of the cecum was suspected in her case, the authors feel that it is likely that she, too, had Whipple's disease. It seems probable that the institutionalized mongoloid brother has tuberculosis, although conclusive diagnosis will probably not be reached prior to death. A younger sister has suffered periodically from myalgia and right shoulder distress, recurrent abdominal pain, constant asthenia and a temporal mandibular arthritis thought to be secondary to malocclusion. She has had a chronic albuminuria for several years. She has also had a persistently flat oral glucose tolerance test and a low fasting vitamin A level. Her prognosis would seem uncertain. The institutionalized maternal uncle developed over a year's time a course characterized by pleural effusion, cardiac enlargement, mediastinal enlargement (probably secondary to adenopathy), increasing serum non-protein nitrogen, elevated erthrocyte sedimentation rate and low fasting blood sugar. He is reported to have died of

coronary occlusion and congestive failure at the age of thirty-seven. A paternal cousin has rheumatoid arthritis. The two daughters of E. V. and another sister have normal oral glucose tolerance and vitamin A tolerance tests.

This instance of proved Whipple's disease in brothers is, in view of the rarity of the disorder, not apt to be accidental. The family history serves to emphasize possible hereditary factors. However, exposure to the same infectious or toxic agent deserves some consideration. No exposure to a toxic agent is known but the family had known exposure to brucellosis and tuberculosis in cattle from which they drank unpasteurized milk. In this regard, tuberculosis with caseation was discovered in a mesenteric node and at the apex of one lung in the patient reported by Christie and Galton, and a caseous node is reported by Whipple.

A survey of the reported cases of Whipple's disease suggests in three ways that a genetic mechanism may be of etiologic significance: (1) The great majority of the cases have been in males. This is overwhelmingly true if challenged cases are eliminated. Although this might be explained by exposure to an agent not encountered by females (perhaps occupational) or by hormonal influences, a genetic factor the expressivity of which varied in the sexes (a not uncommon genetic condition) seems much more likely. (2) All cases thus far reported have occurred in the white race although there has been no special preference for specific nationalities. Lack of exposure to a disease agent encountered by the white race seems unlikely, especially in the United States. Racial immunity seems equally unlikely. The nationality of the patient has not always been stated but when recorded shows no preference. Cases have been reported from Scandinavia, the Continent, Italy, England and South and North America. There has been no specific mention of one of Jewish descent. This situation is strikingly similar to that encountered in non-tropical sprue. (3) All but two cases have occurred after the age of twenty-five. In one of these exceptions (Kampmeir, Case 2) the description of the microscopic pathology is weak and there is no information as to the nature of the material contained within the macrophages described. The other exception (Kampmeir, Case 3) is a thirteen year old girl with clinical and microscopic evidence establishing the diagnosis of lupus erythematosus and Whipple's disease. This consistency in age of the onset of the illness is worth noting since it is common for many hereditary diseases to manifest themselves over a selected age range.

The genetic factor therefore deserves consideration. In the light of presently known cases, the inheritance cannot be explained by a solely dominant, recessive or sexlinked characteristic. In regard to the latter, well established cases have been reported in women. If a genetic factor is involved, it would appear to be dominant with great variability in expressivity and penetrance. The inferred genetic relationship is very similar to that seen in the malabsorption syndrome. Like Whipple's disease, it is most frequently manifested in the white race without national preference, is frequently clinically latent for many years and has a higher incidence in adult life in the male.

Speculation as to the primary defect in this disease and its pathogenesis has been mentioned previously. Determination of several points might greatly clarify the situation. The first point is whether the intestinal absorption defect or the polyserositis is the primary condition. At the time when this might be determined the condition would not be recognizable clinically. Considering the possible hereditary nature of the disease, testing siblings and children of patients seems a logical approach. The secretory and absorption mechanisms of the gastrointestinal tract are the most reasonably tested. This was attempted, with the results previously recorded. More complete studies were performed only on the member showing some abnormality in screening tests and these studies failed to reveal further evidence of disease at this time. The second point concerns establishing the origin of the mucoprotein substance found in the macrophage, although it seems obvious from the distribution that the point of origin is in or through the intestinal mucosa. Of further aid in localizing suspicion to the epithelial cell of the intestinal mucosa is the observation by Frazer[6] of disordered metabolism of intestinal mucin in sprue-like states. The third point is the chemical nature of the mucoprotein and its relation to the increased serum mucoprotein demonstrated by Story and Sagild and confirmed by us. It is granted that some of the material must travel by way of the blood stream to reach the distant peripheral nodes. Were this not true, its presence in these nodes would infer a local origin. However, many other diseases manifest

high serum levels of mucoproteins. Many of these conditions have only inflammation and destruction of tissue in common, such as infarction, infections like pneumonia and meningitis, and malignancies.[17,27] Rheumatoid and Marie-Strümpell arthritis and gout show such elevations,[16] as does vitamin C deficiency in the rat.[21] None of these result in accumulation in macrophages in the distribution typical of Whipple's disease. It cannot at present be inferred that this increased serum mucoprotein bears any particular relationship to that seen within the macrophage.

From the standpoint of pathogenesis we concur in the opinion expressed in full or in part by several recent authors to the effect that the primary defect is probably a metabolic defect of the intestinal mucosal cell, resulting secondarily in a polyserositis as the result of hypersensitivity to a mucoprotein substance. This theory has several implications. Since all abnormal elevations of serum mucoproteins do not result in polyserositis, and since patients with Whipple's disease nearly all have some such manifestations, a difference in the nature of the mucoprotein or the "allergic" nature of the patient is inferred. Since the arthritis (or the pleurisy and pericarditis when symptomatic) is usually the first symptom, this implies a clinically "silent" intestinal defect existing frequently for years before it becomes symptomatic. This lends credence to the conjecture that it may exist from birth.

The possibility of a primary polyserositis triggering a latent intestinal defect, as infection frequently does in sprue, cannot specifically be denied although it has many shortcomings, not the least of which is the observed bowel changes.

SUMMARY

Four cases of Whipple's disease diagnosed between 1943 and 1954 are presented. Case histories of brothers proved to have the disease and extensive history suggesting possible abnormalities in other members of the family is presented.

Diagnosis by peripheral node biopsy is proposed.

It is concluded that pituitary-adrenal factors have no fundamental role in the etiology or fatal outcome of the disease despite the improvement, at least temporarily, of patients receiving ACTH or corticosteroid therapy.

The opinion is expressed that the disease is a hereditary one and transmission is not greatly different from that seen in the malabsorption syndrome. The primary defect is probably a metabolic one localized in the intestinal mucosa.

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Evidence for Serologic Hyper-reactivity in Sarcoidosis*

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VARIATIONS on the theme of the pathogenesis of sarcoidosis have been many but the theme itself has long remained one of host peculiarity. An aberrant individual response has been invoked by those favoring a relation to tuberculous infection[28] as well as more recently by those who have seen a histopathologic similarity between sarcoidosis and "allergic" tissue states such as periarteritis nodosa.[25]

The hypothesis that the host peculiarity might be an immunologic one has frequently been held. Cutaneous anergy to tuberculin,[6] the occasional finding of "anticutins,"[7,14] disturbances of the serum globulins,[29] relative insensitivity in sarcoidosis to BCG,[15] and the frequent modification of the clinical course of the disorder with steroid therapy[27] have all lent weight to this hypothesis. Very recently, two new pieces of evidence relevant to the immunologic aberration thesis have been presented. Friou[1] has demonstrated that patients with sarcoidosis are also less reactive cutaneously to oidiomycin, trichophytin and mumps virus; and Israel et al.[2] have shown the same situation to obtain with regard to histoplasmin.

In further exploration of immunologic considerations, Sones and Israel[3] found that in sarcoidosis there was neither an increased nor a diminished ability to make circulating antibodies to pertussis agglutinogen or typhoid vaccine. Since it has been previously shown by the mismatched blood technic that serologic hyper-reactivity exists in certain diseases in which hypersensitivity is thought to play a major pathogenetic role,[4,5] this method of estimating ability to make circulating antibodies was used to study serologic reactivity in sarcoidosis. The results obtained form the basis for this report.

METHOD

The individuals studied were of three groups: normal volunteers, patients with active pulmonary tuberculosis, and patients with sarcoidosis. The thirty volunteers were composed of presumed normal individuals who were either on duty at Fitzsimons Army Hospital or were awaiting return to duty following convalescence from orthopedic disorders. No other criterion was used in the selection of this group.

The twenty-one patients with active pulmonary tuberculosis were chosen from the tuberculosis wards of Fitzsimons Army Hospital and were tested shortly after admission. They were all bacteriologically proved cases. Fifteen had far advanced, five moderately advanced and one minimal disease. The nineteen cases of sarcoidosis were all proved by biopsy, and other causes of the sarcoid reaction such as histoplasmosis, coccidioidomycosis and berylliosis were ruled out as well as possible by history, cultures, skin tests and agglutination studies.

The normal group and the patients with tuberculosis were tested only on one occasion. The patients with sarcoidosis were given a six weeks' course of ACTH intravenously in the following dosage: 20 mg. over an eight-hour period each day for four weeks, 15 mg. over an eight-hour period each day for one week, and 10 mg. over an eight-hour period each day for one week. The patients were tested before

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therapy was begun and again between the end of the second week and the end of the fifth week of therapy. After ACTH administration had been stopped from one to three months, the patients were retested.

The testing consisted of the intravenous injection of 1 cc. of mismatched blood directly after obtaining a baseline serum sample for isoagglutinin titration. One week later another serum sample was obtained for isoagglutinin titer response to the stimulus of the mismatched blood. Titrations were performed in both saline and albumin diluents. The reasons for employing incompatible blood as the challenging antigen, the dosage used and the technic of titration are contained in a report published elsewhere.[4]

The titer responses of the group of patients with tuberculosis and the group of untreated patients with sarcoidosis were each compared with the titer responses of the group of normal volunteers by means of the "student t" test. This method assumes that the group of untreated patients with sarcoidosis, the group of tuberculous patients, and the normal group all came from the same population. This hypothesis then is evaluated by means of the formula:

$$t = \frac{\bar{X}_1 - \bar{X}_2}{\sqrt{\frac{N_1\sigma_1^2 + N_2\sigma_2^2}{N_1 + N_2 - 2}\left(\frac{1}{N_1} + \frac{1}{N_2}\right)}}$$

where: $\bar{X}$ = arithmetic means of values, σ = standard deviation, N = number of cases. Using a Probability (P) table for "t" with Degrees of Freedom (DF) equal to $N_1 + N_2 - 2$, a "P" value was obtained. A "P" value of 0.05 or less was considered to indicate a significant difference, and 0.01 or less a highly significant difference between the sets of data, thus refuting the hypothesis that all sets were from the same population.

In comparing the titer values for patients with sarcoidosis during and after ACTH administration with the values obtained prior to ACTH administration, each individual was used as his own control. The "student t" test was used, employing the formula:

$$t = \frac{\bar{d}}{\sqrt{\frac{\Sigma d^2 - \bar{d}^2 N}{N(N-1)}}}$$

where: d = arithmetic difference between the value before ACTH, and the values during and after such treatment, $\bar{d}$ = arithmetic mean, N = number of cases. A Probability table for "t" was used with Degrees of Freedom (DF) equal to N − 1. The significance of the "P" value was interpreted as already indicated.

TABLE 1

CHANGE IN ISOAGGLUTININ TITER IN NORMAL INDIVIDUALS FOLLOWING INTRAVENOUS INJECTION OF 1 CC. OF INCOMPATIBLE BLOOD

Patient No.	Saline Titer		Albumin Titer		Fold-Increase	
	Before	1 Week	Before	1 Week	Saline	Albumin
1	56	112	7	14	2	2
2	448	224	112	224	−2	2
3	224	224	14	56	n.c.*	4
4	224	896	14	112	4	8
5	28	56	28	56	2	2
6	224	224	56	56	n.c.	n.c.
7	224	224	224	224	n.c.	n.c.
8	56	224	7	56	4	8
9	112	112	28	28	n.c.	n.c.
10	448	896	56	896	2	16
11	56	224	14	28	4	2
12	1792	1792	896	448	n.c.	−2
13	448	448	112	56	n.c.	−2
14	1792	1792	896	224	n.c.	−4
15	112	112	28	14	n.c.	−2
16	224	224	28	14	n.c.	−2
17	224	448	28	56	2	2
18	28	224	28	112	8	4
19	56	448	14	112	8	8
20	28	896	7	112	32	16
21	224	896	28	224	4	8
22	448	448	14	224	n.c.	16
23	896	448	28	56	−2	2
24	448	1792	56	448	4	8
25	448	448	224	896	n.c.	4
26†	3584	3584	1792	7168	n.c.	4
27	224	448	112	112	2	n.c.
28	224	448	28	112	2	4
29	448	448	112	448	n.c.	4
30	112	448	7	56	4	8

* No change: used in computation as a fold increase of one.
† Not included in computations for valid statistical reasons.

An attempt was made to relate the tissue changes in the biopsy specimens and the clinical symptoms and signs to the fold increases in saline isoagglutinin titer in untreated patients with sarcoidosis. This was done in the following manner: the relative numbers of giant and of epithelioid cells in the biopsy material were each graded zero to four plus, and the sum recorded for each patient. The same was done for relative amounts of fibrosis and of hyalinization in the biopsy specimens. The former elements were taken to indicate activity, and the latter elements were taken to indicate inactivity of the tissue changes. Next, each of a number of common symptoms and signs in sarcoidosis was graded zero to four plus and the sum recorded for each patient. The statistical method used in

TABLE II

CHANGE IN ISOAGGLUTININ TITER IN TUBERCULOUS PATIENTS FOLLOWING INTRAVENOUS INJECTION OF 1 CC. OF INCOMPATIBLE BLOOD

Patient No.	Saline Titer		Albumin Titer		Fold-Increase	
	Baseline	1 Week	Baseline	1 Week	Saline	Albumin
1	27	224	28	224	8	8
2	0*	14	0	7	4	2
3	56	224	14	224	4	16
4	224	448	56	224	2	4
5	1792	896	224	112	−2	−2
6	112	224	56	224	2	4
7	112	112	14	112	n.c.	8
8	896	896	112	448	n.c.	4
9	224	112	28	56	−2	2
10	224	224	56	56	n.c.	n.c.
11	224	112	28	56	−2	2
12	56	224	56	112	4	2
13	112	112	56	112	n.c.	2
14	896	896	224	224	n.c.	n.c.
15	448	896	28	1792	2	64
16	56	1792	0	896	32	256
17	896	896	224	448	n.c.	2
18	448	448	56	112	n.c.	2
19	1792	224	224	224	−8	n.c.
20	1792	1792	224	896	n.c.	4
21	448	896	56	56	2	n.c.

* When the baseline titer was zero and the response titer was 7 the fold-increase was assigned a value of 2; increments above 7 were assigned proportionate values.

correlating the clinical evaluations and the estimates of the tissue changes in the biopsy materials with the fold-increases in saline titer was to obtain a correlation coefficient (r) by the method of least squares. This approach is contained in the formula:

$$r = \frac{\Sigma xy - \frac{\Sigma x \Sigma y}{N}}{\sqrt{\left[\Sigma x^2 - \frac{(\Sigma x)^2}{N}\right]\left[\Sigma y^2 - \frac{(\Sigma y)^2}{N}\right]}}$$

where: r = correlation coefficient, x = numerical expression for clinical evaluation or pathologic changes, y = fold-increase in saline titer, N = number of cases. The value of "r" may vary from plus one to minus one. A value of plus or minus one indicates complete correlation, while a value of zero indicates no correlation at all.

RESULTS

Table I lists the changes in isoagglutinin titer exhibited by thirty normal individuals receiving 1 cc. of mismatched blood intravenously. Table II provides analogous data for twenty-one tuberculous patients. Table III shows similar data for patients with sarcoidosis; nineteen of these patients were tested before ACTH

TABLE III

CHANGE IN ISOAGGLUTININ TITER IN PATIENTS WITH SARCOIDOSIS FOLLOWING INTRAVENOUS INJECTION OF 1 CC. OF INCOMPATIBLE BLOOD

Patient No.	Saline Titer		Albumin Titer		Fold-Increase	
	Before	1 Week	Before	1 Week	Saline	Albumin
1. Before ACTH Administration						
1	224	1792	28	1792	8	64
2	448	3584	112	448	8	4
3	448	3584	28	448	8	16
4	448	11,200	56	112	25	2
5	224	896	28	448	4	16
6	448	5600	224	896	12	4
7	1792	22,400	448	1792	12	4
8	448	3584	112	448	8	4
9	112	448	56	224	4	4
10	224	1792	14	224	8	16
11	56	896	28	224	16	8
12	112	448	14	448	4	32
13*	1792	1792	1792	14,336	n.c.	8
14	28	224	28	224	8	8
15	224	224	28	56	n.c.	2
16	224	1792	56	224	8	4
17	28	448	14	448	16	32
18	896	896	896	224	n.c.	−4
19	1792	7168	112	448	4	4
2. While Receiving ACTH						
1	448	448	224	896	n.c.	4
2	224	224	14	448	n.c.	32
3	448	1792	112	1792	4	16
4	448	3584	56	896	8	16
5	448	896	112	448	2	4
6	....†	.....	.....	.....	...	....
7	1792	1792	112	448	n.c.	4
8	....	.....	.....	.....	...	....
9	112	448	56	224	4	4
10	224	1792	112	112	8	n.c.
11	224	224	112	112	n.c.	n.c.
12	28	896	28	112	32	4
13	....	.....	.....	.....	...	....
14	112	896	56	224	8	4
15	28	224	7	28	8	4
16	....	.....	.....	.....	...	....
17	224	896	224	224	4	n.c.
18	112	448	28	112	4	4
19	....	.....	.....	.....	...	....
3. Following ACTH Administration						
1	....	.....	.....	.....	...	....
2	448	448	224	224	n.c.	n.c.
3	....	.....	.....	.....	...	....
4	448	896	56	224	2	4
5	448	448	56	112	n.c.	2
6	....	.....	.....	.....	...	....
7	....	.....	.....	.....	...	....
8	....	.....	.....	.....	...	....
9	....	.....	.....	.....	...	....
10	896	896	112	224	n.c.	2
11	224	112	14	28	−2	2
12	224	112	56	112	−2	2
13*	1792	14,326	112,000	7108	8	−16
14	224	224	28	224	n.c.	8
15	224	112	7	28	−2	4
16	1792	1792	112	448	n.c.	4
17	3584	448	3584	896	−8	−4
18	....	.....	.....	.....	...	....
19	....	.....	.....	.....	...	....

* Patient not included in computations owing to doubt as to technical and statistical validity.
† Test not performed.

administration, fourteen of the same group were tested again during steroid therapy, and eleven were tested after ACTH treatment. Nine patients were followed by testing at all three periods. Table IV is a statistical data summary chart. Here it can be seen that there is no therapy from the response before such treatment. But after steroid therapy titer response was significantly lower than it had been before therapy, as can be seen by the "P" values in Table IV. Treatment of statistics was difficult owing to the relatively few patients in these

TABLE IV
DATA SUMMARY CHART

	No. of Patients (N)	Saline				Albumin			
		Base	1 Week	Arithmetic Difference (A)	Fold-Increase	Base	1 Week	Arithmetic Difference (A)	Fold-Increase
Normal	29								
Average titer ($\bar{x}$)		354.3	538.8	184.4	3.17	110.6	188.8	78.2	4.14
Standard deviation (σ)		444.	495.	350.	5.98	227.	233.	270.	2.11
Patients with tuberculosis	21								
Average titer ($\bar{x}$)		535.	550.	15.3	2.71	82.7	311.	228.	6.4
Standard deviation (σ)		595.	530.	559.	7.96	84.6	422.	425.	14.1
* Probability (P)		0.25	>.9	0.25	0.7	0.6	0.2	0.15	0.4
Patients with sarcoidosis before ACTH	18								
Average titer ($\bar{x}$)		454.	3721.	3256.	8.72	127.	507.	380.	12.2
Standard deviation (σ)		531.	5500.	5090.	5.92	219.	502.	502.	16.25
* Probability (P)		0.5	<0.01	<0.01	<0.01	0.8	<0.01	<0.01	<0.01
Patients with sarcoidosis receiving ACTH	14								
Average titer ($\bar{x}$)		348.	1040.	692.	6.0	89.5	434.	344.	7.07
Average difference ($\bar{d}$)		−28.0	−2448.	−2420.	−2.64	−21.5	−74.	−36.5	−7.64
† Probability (P)		0.13	0.7	0.15	0.40	0.7	0.65	0.8	0.2
Patients with sarcoidosis after ACTH	11								
Average titer ($\bar{x}$)		851.	549.	−302.	−0.7	425.	252.	−173.	2.5
Average difference ($\bar{d}$)		650.	−1601.	−2251.	−10.5	387.	−33.6	−449.	−9.9
† Probability (P)		0.1	0.15	0.05	<.01	0.3	0.7	0.18	<.05

* Probability of chance difference from values obtained in normal individuals.
† Probability of chance difference from values obtained in patients with sarcoidosis before receiving ACTH.

significant probability that titer responses in the normal and tuberculous groups were different. In contrast, however, patients with sarcoidosis before steroid therapy exhibited saline isoagglutinin titer responses that differed from those of the normal individuals with a highly significant probability, whether judgment is based on absolute rise or fold-increase. Titers based on the use of albumin as the titration diluent showed the same highly significant difference.

There was no significant alteration in the isoagglutinin titer response during steroid categories and the considerable spread of the data; hence, it was believed appropriate to construct Figure 1. Here it can clearly be seen that titer response after steroid therapy was always lower than it had been before therapy.

Table V presents an attempt to give numerical values to the various pathologic changes in the biopsy specimens, and to the clinical symptoms and signs exhibited by patients with sarcoidosis. The degree of correlation between these factors and the pre-therapy fold increases in saline

isoagglutinin titer were then determined. It is obvious from the correlation coefficients in the right-hand column of Table v that no significant degree of correlation exists.

COMMENTS

Many of the previous studies on the nature of sarcoidosis may be regarded as immunologic in implication. Perhaps the first of these was the observation by Schaumann[6] that patients with sarcoidosis are apt to have a negative tuberculin skin test. This observation has been one of the most repeatedly and fully confirmed findings in the history of sarcoidosis.[7–12] Jadassohn[13] construed such lack of cutaneous reactivity into a positive concept of "Anergie," mediated by a specific immune process occurring in the course of tuberculosis. Martenstein[7] gave even

TABLE V

CORRELATIONS OF APPARENT PATHOLOGIC ACTIVITY AND INACTIVITY, CLINICAL ACTIVITY, AND FOLD-INCREASE IN SALINE ISOAGGLUTININ TITER, IN EIGHTEEN UNTREATED PATIENTS WITH SARCOIDOSIS

Patient No.	Giant and Epithelioid Cells*	Fibrosis and Hyalinization†	Symptoms and Signs of Clinical Activity‡	Fold-Increase in Saline Isoagglutinin Titer	Correlation Coefficient of:
1	4	3	10	8	Path. activity vs. path. inactivity: $\sim$ = .16
2	3	0	7	8	
3	5	3	2	8	
4	1	8	7	25	Path. activity vs. reciprocal of path. inactivity: $\sim$ = .11
5	4	2	6	4	
6	4	1	10	12	
7	7	2	7	12	Saline fold-increase vs. path. activity: $\sim$ = .22
8	4	5	7	8	
9	5	4	9	4	
10	5	4	0	8	Saline fold-increase vs. path. inactivity: $\sim$ = .25
11	3	1	2	16	
12	5	1	3	4	
13	2	0	5	8	Saline fold-increase vs. clinical activity: $\sim$ = .24
14	6	7	7	1	
15	6	4	7	8	
16	6	7	5	16	Saline fold-increase vs. reciprocal clinical activity: $\sim$ = .107
17	5	3	6	1	
18	4	4	0	4	

* The relative numbers of giant and of epithelioid cells in the biopsy specimen were each graded zero to four plus, and the sum entered in this column. This column was taken to indicate activity.

† The relative amounts of fibrosis and of hyalinization were each graded zero to four plus, and the sum recorded in this column. This column was taken to indicate inactivity.

‡ Each of a number of common signs and symptoms of sarcoidosis was graded zero to four plus and the total entered in this column. Above 10 was considered marked, 5–10 moderate, and below 5 mild clinical activity.

more exact expression to the concept of anergy by ascribing it to the production of specific anti-tuberculin antibodies which he termed "anticutins." The presence, but neither the specificity nor the role of anticutins in sarcoidosis, was confirmed by Pinner, Weiss and Cohen.[14] Further evidence of "anergy" was offered by Lemming[15] who noted that a negative Mantoux reaction persisted in patients with sarcoidosis who were vaccinated with BCG.

In addition to the peculiar behavior of the tuberculin skin test in sarcoidosis, another kind of aberrant tissue reaction has been reported. In 1941 Kveim[16] showed that ground-up node and spleen material from patients with sarcoidosis produced a nodular lesion when patients with

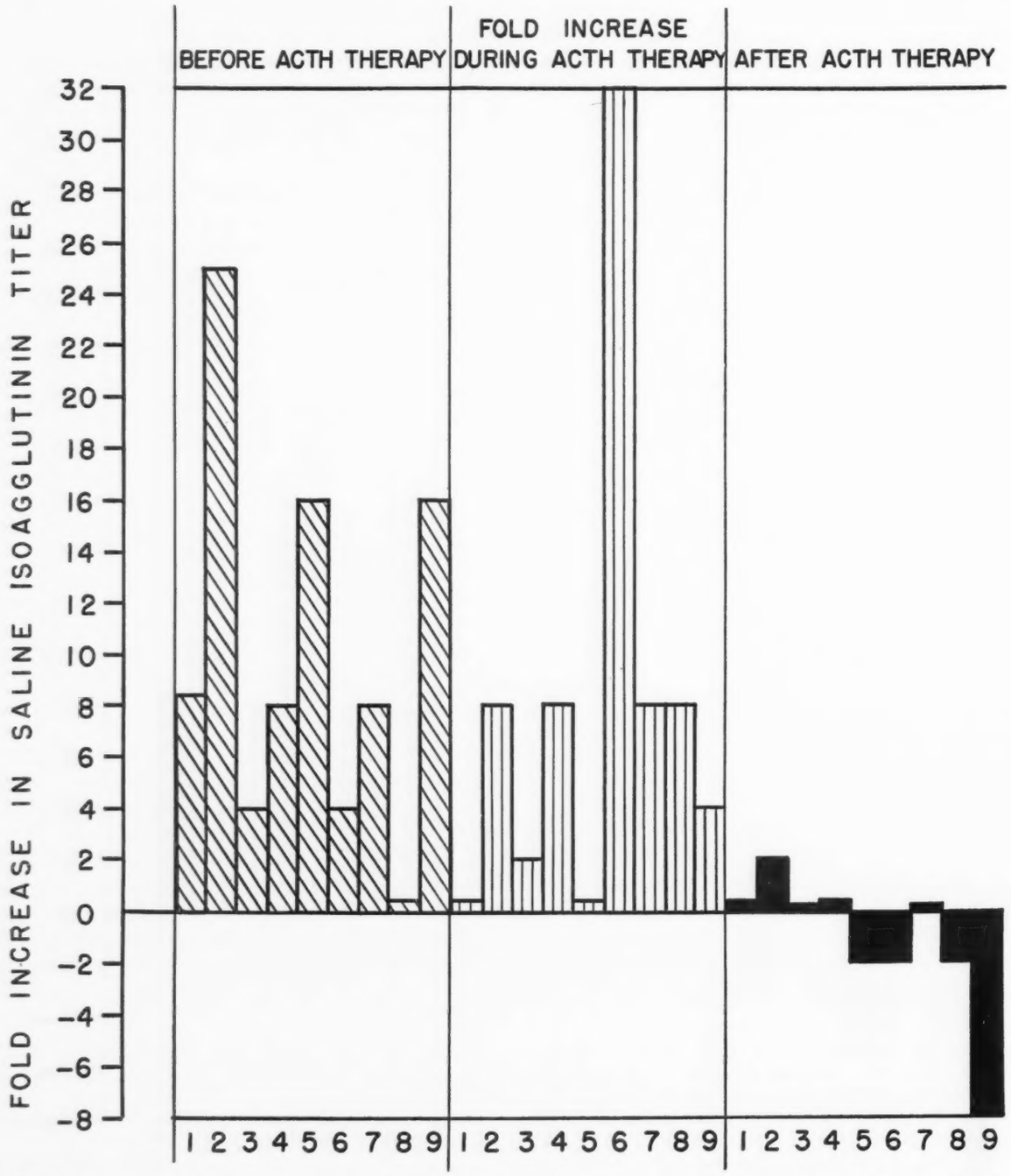


FIG. 1. Decrease in ability to manufacture isoagglutinins following steroid therapy in nine patients with sarcoidosis.

the same disease were inoculated intracutaneously with this material. This lesion, when examined by biopsy several months later, proved to be similar in appearance to those found in sarcoidosis. The finding suggested to Kveim a transferable agent as the cause of the disorder. This conclusion had to be amended following the work of Putkonen[17] and of Nelson[18] who showed that patients with sarcoidosis exhibited this reaction to certain non-sarcoid tissues also. The warranted conclusion has been retained, however, that the tissue responses in sarcoidosis are abnormal.

The essential distinction between inability of the skin to respond when all elements necessary for cutaneous reaction to tuberculin are present, and abnormality of one of the elements themselves was made by Urbach, Sones and Israel in 1952.[19] They found that when patients with sarcoidosis were inoculated intracutaneously with white cells from tuberculin-positive subjects and the site challenged with tuberculin, a positive skin test could be obtained. This was taken to indicate failure, in sarcoidosis, to manufacture or transport antibody rather than inability of the skin to respond.

The concept that the negative tuberculin reaction is in some way specifically related to the pathogenesis of sarcoidosis was finally vitiated by Friou's demonstration that cutaneous hyporeactivity also existed to oidiomycin, trichophytin and mumps skin antigen.[1] This observation was extended by Israel et al.[2] who found skin hyporeactivity to histoplasmin, and also by Sones and Israel who showed skin hyporeactivity to pertussis material.[3] These latter authors[3] also demonstrated a normal skin response in patients with sarcoidosis to intracutaneously administered histamine and to the Prausnitz-Kuestner reaction using ragweed pollen and appropriate serum.

Studies of serologic reactivity lagged behind studies of tissue reactivity. It was not until 1949 that Carnes and Raffel[20] demonstrated that complement-fixing antibodies to multiple antigens prepared from the tubercle bacillus were no different in level in patients with sarcoidosis than in normal, tuberculin-positive individuals. Similarly, Fleming, Runyon and Cummings[21] showed the same situation to obtain using the Dubos-Middlebrook hemagglutination test. At this point in the chronology of studies on sarcoidosis one could say that apparently tissue reactions and serologic reactions in the disease had different implications.

The two serologic studies described concerned static antibody levels obtained at a single point in time. A different approach, measuring antibody response over a period of time following a single antigenic challenge, was employed by Sones and Israel in 1954.[3] Using pertussis agglutinogen and typhoid vaccine they showed that patients with sarcoidosis manufactured circulating antibodies to the same extent as did normal individuals. Our finding of more than normal ability in this regard may be due to the particular antigenic challenge used in this study. The principal reason for employing mismatched blood in measuring antibody reponse in sarcoidosis was the previous experience that this technic demonstrated serologic hyper-reactivity in rheumatic fever and lupus erythematosus disseminatus.[4,5]

Our results indicate that serologic hyperreactivity is a frequent characteristic in sarcoidosis but not in tuberculosis. The kind of serologic behavior in sarcoidosis reported in this paper should be regarded as a characteristic of the disorder analogous to other descriptions, such as changes in serum protein patterns,[23] lack of caseation in the granulomatous lesions[12] or frequency of myocardial involvement.[12] The characteristic described does not in itself directly illuminate the question of the tuberculous etiology of sarcoidosis.

The attempt to correlate titer response, clinical status of the patient and pathologic changes in the biopsy material was unsuccessful. Three possible causes may be assigned for this failure: the members of the group were a non-homogeneous population; the method of evaluating clinical status and pathologic changes was fallacious; no correlation exists among the three elements. It is impossible to evaluate the relative roles of these factors.

The "P" values that express degree of significant difference among isoagglutinin responses of patients with sarcoidosis before, during and after ACTH therapy are listed in Table IV. It can be seen that the titer response after steroid therapy was significantly lower than before such therapy, although the titer response during therapy was insignificantly lower than the response before therapy. Moreover, Figure 1 reveals clearly that in every one of nine patients with sarcoidosis who was tested for saline isoagglutinin titer response before and after

ACTH therapy there was a lower fold-increase value after therapy than was obtained before. In fact, eight of the nine patients showed no fold-increase or a negative value on testing the titer response after ACTH administration. This is especially impressive if one considers that successively higher peak titers are to be expected upon repeated administrations of this antigen.[22–24] It seems a reasonable assumption, therefore, that ACTH was exhibiting its well known ability to curtail to some extent the ability to make antibodies[30] in these cases of sarcoidosis, although it must be admitted that we do not know if normal anamnestic responses are to be expected in this disease. It is tempting but wholly unwarranted to relate this diminution in ability to make antibodies to any therapeutic benefit the patients might have received from steroid therapy.

With the evidence for serologic hyper-reactivity presented in this report, observations on sarcoidosis fall into a strange dichotomy. On the one hand, a tissue abnormality seems to exist involving both a failure of response to certain intracutaneously administered agents and a particular kind of response to others (Kveim reaction); and on the other hand, there is increased ability to manufacture circulating antibodies to at least one challenging antigen. Certainly it is difficult to reconcile the idea of increased ability to make circulating antibodies upon intravenous antigenic stimulation, with hyporeactivity to cutaneous stimuli of an antigenic nature. And when one attempts to fit together increased ability to make circulating antibodies and a peculiar nodular tissue response to many agents one experiences a feeling of irrelevance if not indeed of conflict. One may force an analogy between, say, the serologic hyper-reactivity and particular tissue changes in sarcoidosis, and the serologic hyper-reactivity and particular tissue changes in lupus. But propriety and conviction both seem to be lacking in the analogy. Certain pathologic studies have been thought to suggest a similarity between the appearance and distribution of lesions in sarcoidosis and in periarteritis nodosa.[25] Again, the danger is one of forcing an analogy. Of course, certain aspects of sarcoidosis suggest a pathogenetic relation of the disorder to hypersensitivity. Eosinophilia,[12] disturbed serum protein patterns,[12] amelioration of the disorder when pregnancy supervenes[26] and clinical response to steroid therapy[27] are all circumstantial bits of evidence with a certain cumulative force. The finding presented in this report, of serologic hyper-reactivity to at least one antigenic challenge, is in consonance with the suggestion that hypersensitivity may play a role in the pathogenesis of sarcoidosis. But proof it is not. One must rest content with the observation that serologic hyper-reactivity is a frequent characteristic of sarcoidosis and await the clarifications that future exploitations of such observations may afford.

SUMMARY

1. Patients with sarcoidosis produce significantly higher titers of isoagglutinins in response to the intravenous administration of mismatched blood than do normal individuals. The response in patients with tuberculosis is not significantly different from that in normal subjects.

2. Attempts to correlate titer response with clinical status of the patient with sarcoidosis and nature of pathologic changes were unsuccessful.

3. Not only were anamnestic responses to the antigen not seen when patients with sarcoidosis were tested again after steroid therapy but also in every case the fold-increase in titer was less than it had been before therapy.

4. The significance of the finding of serologic hyper-reactivity is discussed in terms of possible relations of sarcoidosis to hypersensitivity.

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Review

Histoplasmosis*

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SINCE 1945, when Christie and Peterson[31d] and Palmer[146b] reported their remarkable findings concerning the frequency of positive skin reactions to histoplasmin, histoplasmosis has been recognized as a disease of considerable importance. It has been searched for and reported in many parts of the globe but has been clearly demonstrated to be endemic to a significant degree only in the eastern central United States.

It is true that, at present, the chief importance of histoplasmosis rests with the tendency to confuse it with other diseases, particularly pulmonary tuberculosis; however, the rapidly increasing number of correctly diagnosed cases calls for greater appreciation of the potentialities of this disease for morbidity and mortality in its own right. Criteria for the diagnosis of the disease have varied considerably; they should become more strict with increasing knowledge and availability of laboratory facilities. In the endemic area the diagnosis must be considered daily on the indirect evidence of skin sensitivity to histoplasmin in the presence of pulmonary (often calcific) roentgenographic aberrations and a negative tuberculin reaction. It is quite probable that histoplasmosis constitutes the most common cause of "fever of undetermined origin" in childhood in this part of the United States.

This paper represents an attempt to sift and organize the available information concerning histoplasmosis, to evaluate still existent problems and to report seven new proved cases illustrating the variability of the clinical picture.

HISTORY AND EPIDEMIOLOGY

The historical aspects of histoplasmosis have been covered in several readily available reviews[31a,31d,135b,187,188c,212] and will be only briefly recapitulated here. They are so closely related to the investigations of the epidemiology that it is proper and desirable to bring the two headings under joint consideration.

The first recognition of a previously unknown infecting organism was made by Darling in Panama in 1905.[42a] The patient, a twenty-seven year old Martiniquan Negro, had "pseudotubercles in the lungs" and focal necroses in the spleen, liver and lymph nodes at necropsy. In large mononuclear cells in these lesions and also free in the tissues, Darling observed round or oval bodies with refractive rims or capsules. Recognizing that these differed from Leishman-Donovan bodies for which he was searching, Darling suggested the name Histoplasma capsulata (sic) for the new agent. The name apparently was chosen to designate its tissue invasiveness, its resemblance to plasmodial protozoa and its refractive capsule. In 1908[42b] and again in 1909[42c] he reported similar observations in another Negro from Martinique and in a Chinese shopkeeper.

For almost two decades no further reports of the disease were made, and then a few scattered case reports appeared from Austria,[162] Minnesota,[202] Central America,[150] the Philippine Islands[201] and the Dutch East Indies.[137] As to the nature of the organism there was still some doubt, and the diagnoses were based upon the morphology of the parasite in infected tissues

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and on the resemblance to the pathologic data and illustrations in Darling's publications.

Although da Rocha-Lima,[43] from the study of slides of Darling's material, had suggested in a remarkable paper in 1912 the mycotic rather than protozoan character of the organism, it remained for DeMonbreun[47a] and Hansmann and Schenken,[76] independently in 1933, to identify conclusively the organism as a fungus and to describe its cultural characteristics. DeMonbreun's organism was obtained from the blood and tissues of a six-month infant whose clinical course was described by Dodd and Tompkins.[49] In the next twelve years case reports appeared with increasing frequency so that by 1945 Parsons and Zarafonetis[147b] were able to collect seventy-one cases, and shortly thereafter Iams et al.[91b] assembled a total of eighty-one cases. The disease was considered an almost consistently fatal, generalized infection with signs and symptoms depending upon the degree of regional or local involvement. In young children the clinical manifestations were regarded as fever, anemia, marked hepatosplenomegaly, diarrhea, failure to gain weight or weight loss, chronic cough and lymphadenopathy. In adults the features were looked upon as those of systemic infection, sometimes with predominant involvement of a single organ. Chronic granulomatous lesions or histiocytic proliferation in any body organ or system were thought to be the hall-mark of histoplasmosis.

A different concept of the disease arose from studies of non-tuberculous pulmonary calcification in roentgenograms. By the early 1940's it was becoming clear that the incidence of pulmonary calcification in roentgenograms of individuals who failed to react to tuberculin was higher in the east-central United States than elsewhere in the country.[31d,115,155] Noting that individuals from this region not infrequently reacted to relatively concentrated coccidioidin yet did not have coccidioidomycosis, Nelson and Furcolow (1940) speculated concerning other fungus infection as a cause for non-tuberculous pulmonary calcification;[188c] the skin sensitivity to coccidioidin would then be the result of cross reaction to an antigen common to two or more fungi. Smith[188b] confirmed the observations of Nelson and Furcolow and, reasoning from the geographic distribution of the fatal cases of histoplasmosis (the only kind then known), first suggested that H. capsulatum might be the organism responsible. The correctness of Smith's suggestion has received strong support from surveys of sensitivity to histoplasmin, an antigen prepared from cultures of H. capsulatum.[10,31b,146c,153b]

The incidence of positive reactions to this antigen is appreciably greater in the east-central part of the United States than in areas elsewhere in the country, and no other fungus antigen thus far tested approaches it in frequency of reaction. The obvious inference is that, as in coccidioidomycosis, there is a very widespread benign form of histoplasmosis much more common than the fatal form and that this benign form is responsible both for most non-tuberculous pulmonary calcifications and for sensitivity to histoplasmin.

Proof of the presence of mild or clinically silent forms of the disease has been slow in forthcoming. The evidence to 1950 was indirect and based largely on serial studies of pulmonary calcification in histoplasmin-sensitive individuals. Bunnell and Furcolow,[20] in 1948, in a report of ten proved cases of histoplasmosis included one boy of thirteen years as an example of mild illness with recovery. Proof was provided by the isolation of H. capsulatum from one of three gastric washings. The remaining cases were those of severe clinical illness with complete recovery, recovery probable or questionable and progressively fatal disease. Wheeler and his associates[204b] and others[13,108] have reported proved cases in moderately to severely ill children with symptoms and signs referable primarily to the respiratory system. Perhaps the best evidence is the report by Christie[31a] of the culture of H. capsulatum from lesions representing incidental observations in children dying from other causes or, at biopsy, of chronic cervical adenitis. These observations prove that inapparent infection does occur. Why similar observations are so seldom made in areas where the disease is believed to be endemic is by no means clear, unless it is simply a result of the failure to look for or demonstrate histoplasmosis.

Further support for the concept of benign forms of the disease comes from reports of laboratory personnel engaged in the handling of H. capsulatum whose skin sensitivity to histoplasmin changed from negative to positive.[68a] Seven of seventeen such persons in one laboratory had either clinical illness or lesions appearing in roentgenograms of their lungs. Organisms were not recovered from any of those affected. In Sweden[140] seven persons engaged in handling fungus cultures, including a strain of

H. capsulatum, became ill with respiratory symptoms and fever approximately two weeks after the first contact with H. capsulatum. Reactions in all seven subsequently were found to be histoplasmin-positive. Organisms were not recovered from any of the seven but skin tests on other members of the laboratory staff who had not become ill gave negative results, as did those in ten members from a medical department who presumably had had no contact with the organism. In two of the positive reactions, the results were confirmed by one of the authors (J. S.). The incidence of positive reactions is said to be only 0.6 per cent in eastern Sweden (Frisk, cited by Nilzen).[140] In this regard it is interesting that Christie[31a] states: "Among 44 patients in a tuberculosis sanitarium in Northern Sweden and in Swedish medical students, only one individual was positive to histoplasmin. He was born in Southern Rhodesia where histoplasmosis has been found."

An intriguing development has been the discovery[68f] of a possible relationship between infection with H. capsulatum and a series of "epidemics" of unknown etiology having many features in common.[60] Thirteen outbreaks are recognized, and several more are under study,[68a] although in seven of these "epidemics" six or fewer persons were involved. Two of the cases here reported (Cases I and II) constitute infections incurred in a fourteenth "epidemic."[1] Each epidemic was characterized by respiratory illness associated with disseminated pulmonary densities appearing in roentgenograms. Most of the epidemics were related to excavations or dust exposure in areas contaminated prominently by avian excreta or else remotely, if at all, used as human habitation. Attack rates were high and clinical and radiologic features were similar in the several episodes. In only two "epidemics" was the organism obtained from a patient during the acute phase;[1,116a,116b] in all others the diagnosis of histoplasmosis rests on the indirect evidence of positive skin sensitivity to histoplasmin, sometimes positive serologic responses, often the development of disseminated pulmonary calcification in roentgenograms and the isolation of H. capsulatum from soil in the exact area where the exposure is believed to have taken place. Isolation of the organism from soil was accomplished in eleven of the fourteen "epidemics."

This diagnosis in retrospect still suffers from the weakness of circumstantiality. Conversion from negative to positive reactions of skin tests is not assured in all those tested because preillness testing or testing early in the course of the disease was not done. The positive skin sensitivity found for years after the particular illness may have been present prior to it. In one epidemic in which skin test reactions were reported as negative during the acute phase of clinical illness, the incidence of positive reactions in the community in question is such as practically to preclude 100 per cent non-reactivity in any group of adults of the number involved.[170] Accepting the circumstantial evidence for H. capsulatum as the cause of this epidemic, one would necessarily assume that part of the group had exogenous reinfection. The mild cases may have represented some unknown reaction of such a group. Specificity and accuracy of serologic tests are still open to considerable question; the non-specificity of the roentgen shadows are well known. Even the isolation of H. capsulatum from the soil in the areas may indicate only that animals known to have natural infection with the organism had visited the site some time between the epidemic and the time the soil was studied.

Nevertheless, information is accumulating which indicates that the circumstantial evidence may well be correct. The organism has been found in soil in areas where the disease is prevalent[3b] and several different animal species have been found with natural infection in these areas.[129b,129c] The organism has been shown to be able to maintain a saprophytic life cycle in experimentally inoculated soil[58f] and may well do the same in nature. The relationship between rates of pulmonary calcification in roentgenograms and rates of histoplasmin sensitivity is so clear cut no one can deny that whatever causes the one must in large measure cause the other, and no organism other than H. capsulatum has been recovered consistently wherever the disease has been suspected.

GEOGRAPHIC DISTRIBUTION

Information concerning the geographic distribution of the disease comes from case reports and from surveys of sensitivity to histoplasmin.[133] Many reports are open to question so that in certain regions it is not yet proved that histoplasmosis is endemic. Nevertheless, it is safe to say that the disease is present in Africa, North, South and Central America, and possibly in some Asiatic islands and in Europe. Information from the Asiatic mainland and Australia is, at

present, inconclusive or else indicates absence of the disease. One case has been reported from New South Wales, Australia, diagnosis resting on histologic examination[95] of an excised skin nodule.

The area of greatest incidence is undoubtedly in the East Central United States. This includes the states of Missouri, Tennessee, Kansas, Kentucky, Illinois, Iowa, Ohio and Indiana. Sensitivity to histoplasmin falls off in all directions away from this contiguous cluster of states, and rates of sensitivity tend to vary inversely with the distance from this area. Unexplained local variations in the frequency of skin sensitivity occur even within narrow geographic limits of states, counties and cities.[68k,68l] Reports of cases and histoplasmin reactions are known in Canada[73d,74a,74b,191a] but the frequency is much less than in many areas of the United States. The southeastern provinces, those nearest the endemic area in the United States, are the ones from which the reports arise. No significant histoplasmin sensitivity has been found in Alaska.[183]

Mexico and the Central American countries show a relatively high histoplasmin sensitivity rate.[52a,84,181,198a,199b] Darling's three cases were found in Panama between 1905 and 1907, but none was in a native. No further reports of the disease there appeared for forty-five years[198b] except for one case of canine infection in 1945.[197] In 1951 a survey of 1,000 persons revealed 387 positive reactions to histoplasmin, of which 310 were also positive to tuberculin. Pulmonary calcification was found in roentgenograms of 113 persons.[198b]

In South America, too, relatively high frequency is noted but marked variations are observed from country to country and in different regions in the same country. Brazil[25] and Argentina both have areas of high incidence.[8,71b] A proved case has been reported from Chile[142b] where sensitivity rates thus far reported have been low.

The few reported surveys from India and China[133] indicate no significant incidence of histoplasmin sensitivity. A few reports from widely scattered areas in Africa show a low but definite incidence of histoplasmin sensitivity.[118]

In general, surveys from European countries, with the exception of Italy,[193] show very little or no histoplasmin sensitivity.[71a] Recent reports of clinical cases from France,[94] England,[40,48] Norway,[15] the Netherlands[177] and the Mediterranean countries[26,209] are based largely on circumstantial evidence of infection or else may easily represent imported cases from endemic areas.

It has been suggested by several investigators that areas of high incidence have in common a geologic situation of large rivers running through low countries.[164] However, there are numerous exceptions and, although humidity and dampness may be factors in perpetuation of the disease, other common features remain to be discovered before reasons for the geographic localization of H. capsulatum can be defined.[211b]

What is not known about the disease constitutes a challenge of considerable proportions for further investigators. It is not known whether there is any seasonal incidence. The reasons for the geographic distribution are unknown. Several[163,211b] have speculated concerning the effects of humidity, dampness of the soil, chemical composition of the soil, and so on. The portal of infection is not proved completely, although the evidence from a few well studied cases[110b,178a,178c] is very strong that, as in tuberculosis, it is largely respiratory. Rare primary lesions in the gastrointestinal system or in the skin or mucous membranes cannot be excluded and in some case reports appear to be probable. Transmission from human to human or from animals to humans has not been demonstrated; transmission from animal to animal (dog) has been suggested by studies of Prior and Cole.[153c] On the other hand, thirty-five male mice kept in plastic cages with infected females for two to six weeks gave negative reactions without exception (authors' unpublished data). The disease is so asymptomatic that man-to-man transmission may easily escape detection. From results of skin tests in cattle[68m,128,129f] it has been inferred that animals and humans in the endemic area obtain the infections from similar if not common sources. Studies of skin sensitivity among siblings[63b] suggest that factors outside home contacts are responsible for positive reactions in several members of a family.

HISTOPLASMOSIS IN ANIMALS

Histoplasmosis in dogs was first observed by DeMonbreun.[47b] Numerous instances in dogs and in different species have been found but the main point, whether or not there is any relationship between animal and human histoplasmosis, is still largely unanswered.

H. capsulatum has been demonstrated in cats,

mice, rats, skunks, foxes, opossums,[58a,c,d,e] bear,[39] raccoon,[129d] frequently in dogs,[34a,34b,128,129a,129b,129c,129e,153d] cattle[129b,129f] and possibly in a ferret[111b] and two horses.[157,162] H. capsulatum has been demonstrated in 44 per cent of fifty dogs and of fifty cats collected at random in Virginia.[169b]

Positive skin test reactions in animals are often obtained with concentrated or only slightly diluted antigen. Experimental infection seems to indicate certain specificity even of concentrated antigens; nevertheless one cannot fail to mention that, in general, with decreasing dilution the specificity of skin test antigens decreases. With this in mind, one can take notice of positive skin test reactions obtained in cattle, sheep, horses, swine, fowls, dogs and other animals.[34a,128,129c,129d]

With undiluted antigen, the skin tests of approximately eighty monkeys, maintained in a local research institution for periods of four months to three years, failed to elicit a single positive result. The animals had limited exposure to the endemic environment in an open "monkey island" in the local zoo during the summer months. The skin tests were performed on the upper lids of the animals (authors' unpublished data).

For obvious reasons wild animals cannot acquire the disease from man and are unlikely to be carriers directly responsible for human disease. It then becomes logical to assume that wild and domesticated animals acquire the disease from soil in a manner analogous to man; the cat, which comes in close contact with mice and rats, could possibly become infected from rodents.[58a]

Only the future will show whether the high incidence of positive skin test reactions in certain animal species really represents an expression of infection with H. capsulatum. In the first place, heterogeneous antigens and variable dilutions have been used in the different series, and comparison is hardly possible. Besides, it is well known that certain animals (mice, rats) hardly ever show positive skin test reactions while others react very strongly. It then becomes—until anatomic studies corroborate the skin testing—a matter of guessing whether, for instance, the high incidence of positive skin test reactions in horses (65 per cent)[129b] represents a true antigen-antibody reaction or whether other factors intervene.

Little has been published about the pathology of spontaneous histoplasmosis in animals[164] but excellent papers are available about cytology[16b] and other findings in experimental animals.[44,86e,106b,174] Monkeys[47b,210] golden hamsters,[53,159] mice,[47a,86e,106b,113a,147a] rats,[130] dogs,[61,129e] gerbils[16b] and guinea pigs[28,160] have been used in experimental work with uniformly positive reactions. In rabbits, however, results are equivocal.[28,77b,159] We found the mouse to be the animal of choice. Intravenous inoculation results in 100 per cent mortality, with an average life span of twenty-eight days in young male mice. Other authors favor intraperitoneal injections with or without mucin but results are never so constant or uniform as with intravenous inoculation. Schaefer[173] studied the influence of age on experimental histoplasmosis.

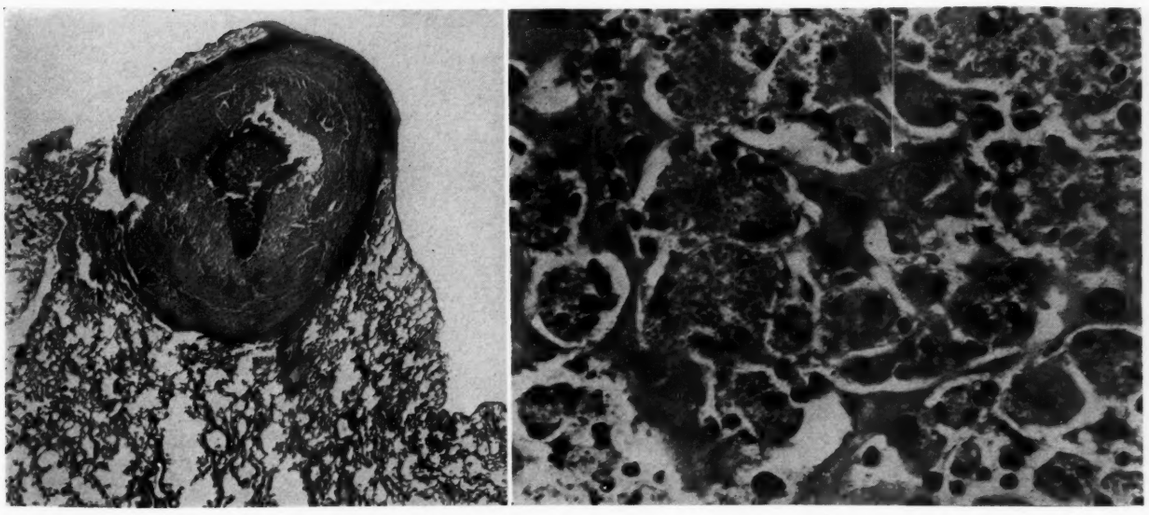
Intracerebral inoculation seldom produces lesions outside the brain.[101b] Brandt[16a] demonstrated the positive influence of x-ray radiation prior to inoculation on dissemination. Cortisone did not influence the course of experimentally inoculated disease in mice[9] but made dogs susceptible to infection.[61]

Interestingly enough, gross inspection of experimental animals from which H. capsulatum can be isolated often does not show any abnormality, one of the many intriguing diagnostic problems of the disease in animals. In three spontaneous cases in dogs a typical primary complex was found in the lungs and mediastinal lymph nodes. (Fig. 1.) While spleen and liver (Fig. 2) represent the best source for culturing from experimentally infected animals,[86c,106b] blood smears and cultures may sometimes be helpful. The former especially can give quick information about the number of circulating organisms. H. capsulatum has been isolated from urine of guinea pigs[159] and feces of dogs.[153c] As little as a single organism is sufficient to infect experimental animals (mouse).[3a]

Attempts to immunize mice have been reported recently;[171h,173] the immunity is relatively short lived.

SEROLOGY

The experience with serologic methods in the diagnosis of histoplasmosis has not advanced to a point where constant and unequivocal results can be anticipated. The reasons are as follows: (1) Too few verified active and progressive cases have been tested adequately to permit definitive conclusions; (2) several partially conflicting technics are in use which possibly reflect the



1 2

FIG. 1. Primary subpleural focus in spontaneous histoplasmosis of dog; central calcification; thin fibrous capsule; positive culture from satellite lymph node; original magnification × 28.

FIG. 2. Experimental (intravenous) infection; mouse liver; enormous swelling of phagocytes containing multiplying organisms; original magnification × 650.

response to different antibodies rather than to poor technic *per se*, and (3) very few laboratories do reliable, easily available tests.

The following technics have been described: complement fixation with an antigen from formalin-killed yeast cells,[171f] mycelial-phase broth filtrate (histoplasmin),[68d,171j,176,194] heat-killed whole cells[172c] and extract from ground yeast cells.[22e] Saslaw[172b] developed, in addition, a collodion agglutination test. While most observers agree that a positive serologic reaction with high titer may be found in active and progressive cases, contrary experiences have been recorded in which no antibodies could be detected in spite of progressive histoplasmosis[20,172a] or in spontaneously infected animals.[58e] Grayston questions whether prognostic significance can be attributed to the histoplasmin complement fixation test.[72a] Cross reactions, especially between histoplasmosis and blastomycosis[171b,d] and to lesser degree with coccidioidomycosis, have been observed both in naturally occurring disease and in sensitized experimental animals.[22b,c,58g,86b]

For practical purposes we believe that the presence of a positive complement fixation test at levels considered critical by the specific laboratory where the test is performed warrants further clinical and cultural investigation. The suspicion of active disease will certainly arise if the titer of the serologic reaction should be rising on serial tests. However, the importance of performing the tests on sera obtained at different periods of illness, if at all possible on one day, using identical conditions and antigen, cannot be overemphasized. We are at a loss to recommend one method in preference to any other; a negative serologic reaction, like any other negative reaction, does not rule out histoplasmosis.

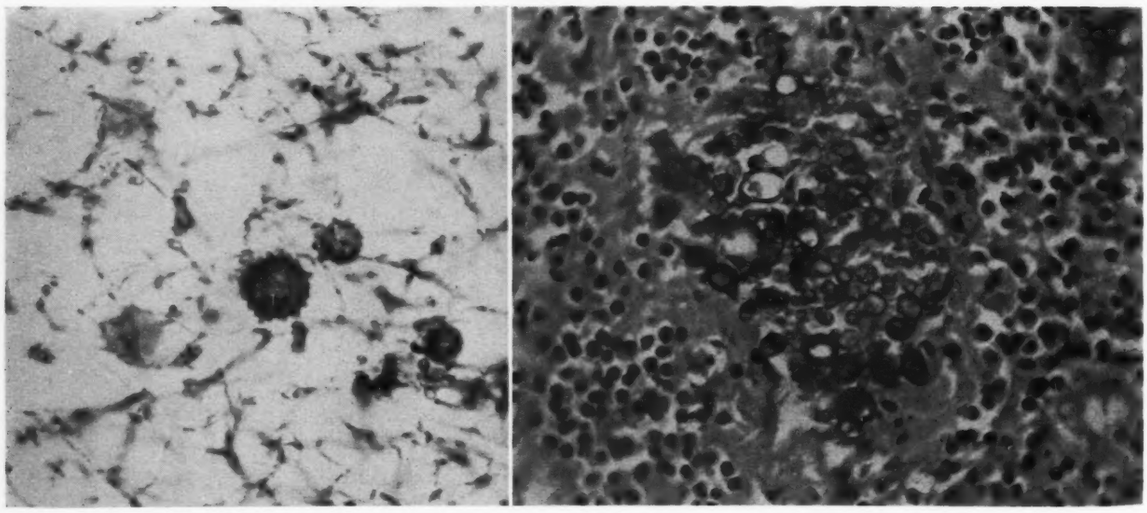
Cross reactions are common[171b,d] but can be easily detected if at least a blastomycin complement fixation test is run simultaneously. Whether or not a rising titer indicates dissemination and a falling titer improvement has not been established in a sufficient number of cases; exceptions are not uncommon. Attempts have been made to separate fractions of the antigen which would react with early or late cases only or which would not cross react, but this has been done only on a small number of sera.[22c]

Tests based upon the precipitin reaction[148,171i] and agglutination of sheep erythrocytes[142] have not passed into general use.

MYCOLOGY

Histoplasma capsulatum belongs to the Moniliacae of the Fungi Imperfecti[35] and is a biphasic fungus which, in tissue and on culture media kept at 37°C., appears as a small yeast (parasitic phase). At room temperature a mold develops (mycelial or saprophytic phase).[35,47a,86a]

The colony, after six to ten days on Sabouraud's dextrose agar, is small, white and cottony in appearance. The colony enlarges fairly fast



3 4

FIG. 3. Tuberculated spores at room temperature are pathognomonic for Histoplasma capsulatum. Small spores are seen elsewhere in the picture; original magnification × 1000.

FIG. 4. Case II; lymph node; giant forms in tissue explants. Compare size of organisms with lymphocytes. Original magnification × 650.

and becomes slowly tan to dark brown in back. A culture mount after two to three weeks (needed for the development of the tuberculate spores) reveals: (1) small spores which are sessile or on a short stalk and measure 1 to 5 μ.; these spores are smooth and spherical to pyriform; (2) larger round or ovoid smooth spores of 5 to 20 μ. often on short stalks; (3) tuberculate spherical to pear-shaped spores, which measure 10 to 25 μ. and are considered by modern authors to be aleuriospores.[58f,86a] (Fig. 3.) The latter are characteristic and resemble the medieval mace. The "projections" have been adequately described as thin points in the wall of the spores with cytoplasm pouring through the weakened spots in the wall.[51,86a]

The hyphae are generally thin. Septate and occasionally racquet mycelia are observed. The latter are found more often in cultures changing from the yeast phase to mycelial growth than in cultures kept constantly at room temperature. The number but not the diagnostic importance of the tuberculate spores has been overestimated in the past.[37,79] Certain strains from Georgia had very few tuberculate spores.[58e] Since particle size has been shown to be of importance in penetration into the alveoli of the lung,[18,19] it is indeed of interest to establish which spore size is prevalent.

Blood agar (found most efficient for growth from animal organs[86c]) can be used in addition to Sabouraud's medium, broth and corn meal agar for isolation of the fungus. Growth of the yeast phase is possible in liquid media; a small amount of agar (0.175 per cent) and a pH of 6.3 to 8.1 are essential.[171e] Even one drop of blood on the surface of Sabouraud's medium changes completely the growth character of the fungus which then appears flat, waxy gray-brown and without visible aerial mycelium.

H. capsulatum grows with ammonium as the sole nitrogen source and a sulfide or sulfhydryl group in a small organic molecule is essential for growth in the yeast phase. The presence of biotin is necessary for the yeast phase but has no effect on mycelial growth. Even at 37°C. change of phase can be accomplished by variation of culture media.[171g] The ideal pH is said to be between 7.2 to 7.6[38,86d] or 6.5 to 7.5.[86a]

On blood agar at 20°C. the appearance of the fungus is quite different from the appearance on Sabouraud's medium. The colony seldom becomes cottony, is gray, small, rather firm and leathery and sometimes has a slightly fluffy center. Tuberculate spores do not develop with the constancy which one expects on Sabouraud's medium. At incubator temperature the colony is slightly warty, dry-creamy or bacteria-like if growing profusely. Multiple budding of yeast cells has been described.[51]

Littman's oxgall agar does not support the growth of all strains and should not be used for primary isolation except in combination with the media already mentioned.

Conversion from the yeast phase to mycelial growth never fails but it is often difficult to convert mycelial growth with regularity to yeast without recourse to animal inoculation. Heavy inoculum, sealed blood agar slants (with or without cystine) and temperatures ranging from 34°C. to 37°C. are prerequisites for the change of phase, which may take as long as seven to ten days to develop.[125] Frequent subcultures (four to six days) are in general necessary to maintain growth in the yeast phase on solid media. Egg-yolk potato medium maintains yeast growth for long periods.[109,196] Once yeast growth has been induced in broth, maintenance is much easier, even if simultaneous mycelial growth may appear on top of the liquid. Rapid mass production on relatively simple media can be considerably enhanced by shaking action.[171c] H. capsulatum has been grown successfully on the chorio-allantoic membrane of the chick embryo.[103,135a]

An endotoxin has been described lately by Salvin.[171a]

The fungus is very resistant to physical exposure. It has been kept for four months in dried sterile soil, in water, ice (for over a year) and is reported as viable after heating at 62°C. to 63°C. for ten minutes[11b] or 45°C. for thirty minutes.[47a] The foregoing information would seem to suggest the necessity of public health measures to prevent burial of human or animal victims of the disease in view of the well founded belief that the soil constitutes a frequent source of infection. Certainly cremation would solve this problem.

The organism has been repeatedly seen in[58f] and recovered from soil by cultural or inoculation methods.[3b,58f,68i,72b,119,180a,211a] Lately it has been isolated from air in two areas which had given origin to outbreaks (epidemics) of histoplasmosis[92] and from an air sample in Iowa City.[168]

The morphology of the organism in culture mounts, in blood smear and in tissue is greatly influenced by the staining methods. With lactophenol cotton blue in the culture mounts, the fungus has partially stained cells; details about the sudanophil content are described by Howell.[86a] In the blood or bone marrow smear stained with the Wright stain or with similar stains, a pale bluish ring with focal chromatin generally is seen on one narrow side of the ovoid body and often the pigment is crescentic in shape. In tissue, with hematoxylin-eosin, small central dots surrounded by a pale halo are seen. Very seldom the ring form observed in blood smears can be reproduced in tissues with hematoxylin-eosin. If desired, a section stained with hematoxylin-eosin can be stained with periodic acid-Schiff stain without intermediate steps; the periodic acid decolorizes adequately.[103] With Schiff's reagent, using either the Hotchkiss-McManus or the Bauer stain, small red dots surrounded by a red thin ring or empty ring forms are visible. Occasionally, a disc-like figure a few micra in diameter can be seen representing the organism. Most authors agree that H. capsulatum has a capsule;[42c,58b,86a] a few deny it.[3c,103]

Budding is rarely seen in tissues or blood smears, in contrast to Blastomyces dermatitidis or Monilia which produce abundant budding forms in animal tissue. Larger forms have been observed occasionally in old blood kept in storage,[11b,67] and the organisms appear in general larger with the Hotchkiss-McManus stain[58f] because the whole cell is stained including the part which in hematoxylin-eosin stains seems to represent the capsule. Large forms of smooth outline have been produced lately in tissue explants from human and animal sources. Probably some factors producing tissue decay are connected with the development of the large spores.[180c] (Fig. 4.) Large forms have been seen repeatedly in Africa and a distinct species has been proposed by Vanbreuseghem as H. duboisii.[28,33,55,100a,b]

In retrospect, it is difficult to understand why culture of the organism was not accomplished until about thirty years after the discovery of the organism by Darling, since no special difficulties are encountered.

HISTOPLASMIN

The filtrate of cultures of H. capsulatum grown for several months in a synthetic broth[58g, 86b] is used as antigen for skin testing. At present there is no purification of the antigen but standardization is attempted by titration in human beings or infected guinea pigs, taking Howell's original histoplasmin H-15 as standard.[185] Considering Howell's original 1–1,000 dilution of H-15 the "standard," it is possible to select single or pooled antigens which at a given dilution react similarly to the 1–1,000 dilution of H-15. Unfortunately, it is not made clear in many papers dealing with skin sensitivity studies whether given dilutions are comparable to the H-15 standards or are purely arbitrary. It would be imperative to have this

point clarified in the future in order to permit comparison of results obtained from antigens of different provenience.

The "ideal" antigen at critical dilution will give a minimum of heterologous skin reactions and an optimal number of homologous responses. The specificity may not apply to the same antigen when used for serologic reactions in the test tube. The question of specificity is indeed of prime importance. While there is no cross reaction with tuberculin, it has been shown both in men and experimental animals[58g,68l,86b,188a] that cross reactions do occur between histoplasmin and blastomycin, and to lesser degree also with coccidioidin and haplosporangin. Appropriate dilution of an antigen in general produces practical and useful results. Thus, for obvious reasons, the actual skin testing with histoplasmin should always include at least one other antigen, preferably blastomycin. In a recent survey it was shown[68l] that about a third of positive histoplasmin reactors also reacted to blastomycin and occasionally the reaction to the latter was larger in diameter than to histoplasmin. Experimental Candida albicans infection produced cross reaction to the histoplasmin skin test.[124]

Concentrated antigens are much less specific than diluted ones. Unfortunately, in certain animals (dog, cattle, horse) only relatively undiluted antigens (1:5, 1:10, 1:100) elicit skin reactions. In certain animal species (mice), skin reactions in experimentally infected animals can hardly ever be elicited whereas the guinea pig readily responds to intracutaneous testing.

In man the test is performed by intradermal injection of 0.1 cc. of antigen diluted to correspond to 1:1,000 of the original antigen of Howell (H-15). Any induration of 5 mm. and more is read as positive. Measurement of the induration and erythema is desirable. Erythema without induration is only rarely observed and should not be read as a positive reaction. Forty-eight hours after injection is usually accepted as reading time. A few reactions present at twenty-four hours disappear at forty-eight hours. On the other hand, true induration may become apparent after seventy-two hours or even later. In a survey, reading at forty-eight hours can be instituted arbitrarily and all other reactions can be neglected. In individual testing, it can become quite difficult to decide whether a transitory induration present at twenty-four hours and absent at forty-eight hours should be read as positive or not, and the same applies to reactions which appear after forty-eight hours.

It is generally assumed that a positive skin test in human beings represents a local demonstration of antibodies, indicating past or present infection. What is the evidence to support the assumption that a positive histoplasmin reaction means past or present infection?

1. It has been shown beyond any reasonable doubt that a positive reaction to the coccidioidin skin test with a dilution of 1:1,000, if given properly with appropriate antigen, signifies past or present infection with Coccidioides immitis. Since normal laboratory animals never show positive skin reaction to histoplasmin and since the development of a positive skin test can be observed after inoculation of Histoplasma, it seems permissible to consider the histoplasmin test as analogous to the coccidioidin test.

2. Many patients with proved histoplasmosis have a positive skin reaction to histoplasmin. By implication then, it is believed that a positive reaction occurs in persons who have or have had the disease.

3. Again as in the case of coccidioidomycosis, in which subclinical forms have been demonstrated to exist in apparently healthy individuals, it is suspected that asymptomatic histoplasmosis occurs. This belief is based on the prevalence of positive skin reactions in regions where clinical cases are most frequently observed, on the fact that animals in these areas have both positive skin reactions and clinical disease, and last but not least on the frequent observation of pulmonary calcification in tuberculin-negative persons with positive histoplasmin reaction.

Proof that subclinical forms of histoplasmosis exist is, at present, largely indirect. For completeness, it is necessary to enumerate the possible arguments against the conclusion that subclinical forms of histoplasmosis exist.

1. Incidental observations of asymptomatic histoplasmosis should be much more frequent at autopsy than actual experience seems to indicate. Whereas tuberculin-positive persons in the United States are decreasing regularly in number, occasional active and, more frequently, inactive foci are found at autopsy. The latter are thought to represent old, burned-out tuberculous lesions. Active foci of histoplasmosis have very seldom been observed as incidental findings, even in areas where the histoplasmin sensitivity rate is 70 per cent or greater. It is possible that an unknown number of calcific

pulmonary lesions which are classified as tuberculous are in fact due to histoplasmosis. Culture or histologic demonstration of H. capsulatum in calcified lymph nodes or burned-out lung lesions seldom has been accomplished (Ref. 31*a*, 58*g*, authors' Case VII) It is only fair to say that acid-fast bacilli are not demonstrated in every calcified focus. The possibility of such foci being of mycotic origin does exist, once more having in mind analogous findings in coccidioidomycosis[36,188*e*] and blastomycosis.[182*d*]

2. In only a relatively few of the proved cases of histoplasmosis have the patients had skin tests and not all have given positive reactions. Anergic reactions in severely ill patients are known in other diseases and may also occur here.

3. Large surveys have shown that a certain number of persons with calcified chest lesions do not react to any known antigen. From this finding we may conclude that calcified intrathoracic lesions occur independently in tuberculosis, histoplasmosis or coccidioidomycosis. It is only one step further to claim that all calcifications which are not due to tuberculosis are of unknown origin. Since a considerable number of persons with calcified lesions gave positive reactions, both to tuberculin and to histoplasmin, a specific answer in a given case may be beyond our present knowledge.

4. Clinical cases are rare or lacking[143] in surveys in areas where a high incidence of histoplasmin reactions exists, even where clinical cases have been found in men and animals.[153*d*]

5. The cross reactions may lessen the significance of skin or serologic testing. It has been shown that animals which are infected with Blastomyces may react strongly to blastomycin but, at the same time, to histoplasmin, coccidioidin or haplosporangin. This point must be considered in some detail.

Obviously, a positive reaction to different antigens brings several possibilities to mind. Either there is a common (partial) antigen in the four studied antigens (blastomycin, coccidioidin, haplosporangin, histoplasmin), or metabolic products of fungi are fairly similar in all four molds, or there may be an unknown factor which is responsible for the positive reactions. The probability of a common antigen is likely since no reaction can be elicited in healthy animals or healthy persons whereas in infected individuals cross reactions do occur.

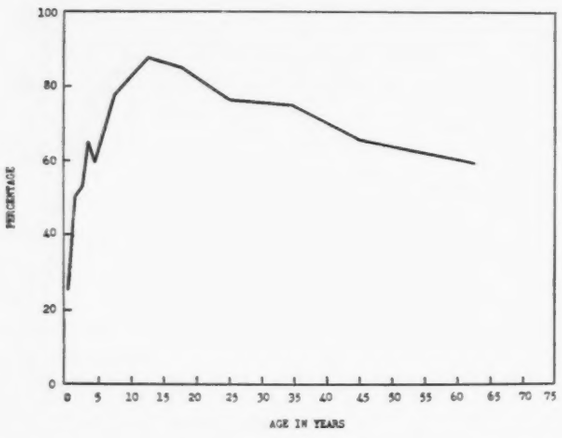
The fungi are not more antigenic than are their metabolic products. It has been demonstrated that addition of ground mycelia to the filtrate does not change the reaction or selectivity of the antigen. Obviously, heterogeneous organisms may have similar metabolic by-products and these metabolites serve as antigens. If there should be an unknown or neglected fungus which is responsible for the positive skin reactions in regions where calcified pulmonary lesions are common and tuberculosis may be excluded, this new fungus could possibly be responsible for skin reactions which now are read as positive for histoplasmosis.

Another observation which is very hard to explain is the decrease of positive reactors to histoplasmin in old age[211*b*] (Fig. 5) and the loss of reactivity which has been observed in specific individuals. It has become obvious that other skin reactions (tuberculin, coccidioidin) also become weaker or disappear with an increasing time interval between infection and testing. Why, however, in histoplasmosis the positivity of skin reactions decreases after forty years of age is not understood. Zeidberg,[211*b*] Furcolow[68*e*] and others have had considerable experience with retesting of individuals; alternating reversals of skin reactions have been observed even in proved cases. (Fig. 6.)

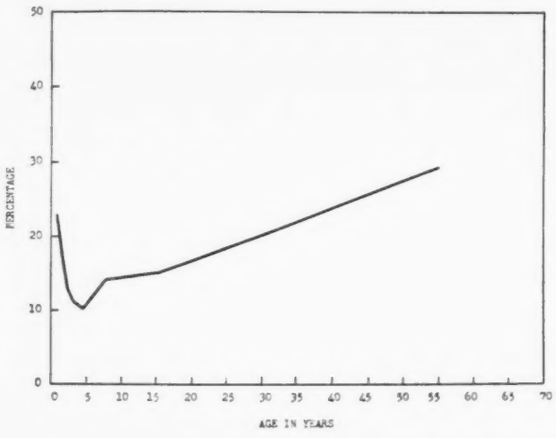
For practical diagnostic work, the importance of the histoplasmin skin test can be stated in the following way: A positive reaction to the best of our knowledge means past or present infection with H. capsulatum; a negative reaction does not rule out infection especially in severely sick patients.[200] There is still too little experience with the reaction in children of pre-school age to permit statements about the importance of negative reactions in this age group. Much of the discussion about the prevalence and distribution of histoplasmosis is based on results of skin testing. Lack of standardization of the antigen detracts from the reliability of certain results but in general it appears quite conclusive that: (1) High rates of skin reactors can be found mainly in Ohio, Iowa, Kentucky, Indiana, Kansas, Missouri, Tennessee and southern Illinois, and coincide with the geographic distribution of symptomatic cases. (2) Pulmonary calcification in the states indicated is more often associated with a positive histoplasmin reaction than with a positive tuberculin reaction. (3) Persons who gave negative results and were exposed to infection either naturally or in laboratories convert from a negative to a

positive skin reaction. (4) Certain infected animals convert, while to the best of our knowledge laboratory animals which had no contact with H. capsulatum never give a positive reaction.

For the sake of completeness it should be mentioned that a report of questionable significance has appeared with respect to positive reactions in penicillin-treated patients.[56]



5



6

FIG. 5. Typical frequency curve of histoplasmin sensitivity in relation to age. (From ZEIDBERG, L. D., DILLON, A. and GASS, R. S. Some factors in the epidemiology of histoplasmin sensitivity in Williamson County, Tennessee. *Am. J. Pub. Health*, 41: 80–88, 1951.)

FIG. 6. Incidence of reversal of skin test from positive to negative. (From ZEIDBERG, L. D., DILLON, A. and GASS, R. S. Some factors in the epidemiology of histoplasmin sensitivity in Williamson County, Tennessee. *Am. J. Pub. Health*, 41: 80–88, 1951.)

PATHOLOGY

The pathology of histoplasmosis is protean and, while a general pattern can often be recognized, no two cases follow precisely the same course. The parasite is usually found in phagocytic cells and for this reason, in generalized disease and in the experimental animal, liver, spleen, lymph nodes and bone marrow are filled with organisms.[2,103,151a]

Generally speaking, three reactions can be recognized in response to invasion of the organism by H. capsulatum. First, isolated organisms may be found in phagocytes with minimal or no tissue reaction of any form. Such observations are generally accidental or may be seen in lymph nodes which are at a considerable distance from the focus of inflammation. Frequently some nodes of the chain show more impressive reactions.

Second, often associated with a larger number of organisms marked histiocytic proliferation can be found which is most prominent in lymph nodes (Fig. 7), liver and spleen. Sometimes also whole alveoli in the lung can be seen filled with phagocytes containing numerous organisms. The sinusoids in lymph nodes in such cases may be completely obliterated, and beginning or progressive necrosis may be present.

Third, the granulomatous form can be observed. This occurs either in the productive (tubercle forming) or the exudative (caseating) variety (Fig. 8) and the two varieties may be seen simultaneously in the same organ or in different organs of the same individual.

Primary Pulmonary Complex. From observations in the literature and from our own experience in human and animal cases of histoplasmosis we conclude that the respiratory organs are the most common site of primary infection. In addition to the anatomic data, which will be discussed more extensively, there are also the epidemiologic facts which speak very much in favor of a respiratory portal of entry. We have in mind the epidemic outbreaks of the disease[60,68b,72c,116a,119] and the laboratory infections.[68g,140] In man, Schulz in two excellent papers[178a,178b] has described the appearance of primary pulmonary complexes which in every respect can be compared with tuberculous foci, that is, in size, shape and localization. Careful dissection and histologic examination of lungs from 105 consecutive autopsies in the endemic area revealed H. capsulatum in seventy cases with healed primary complexes.[191b] This figure

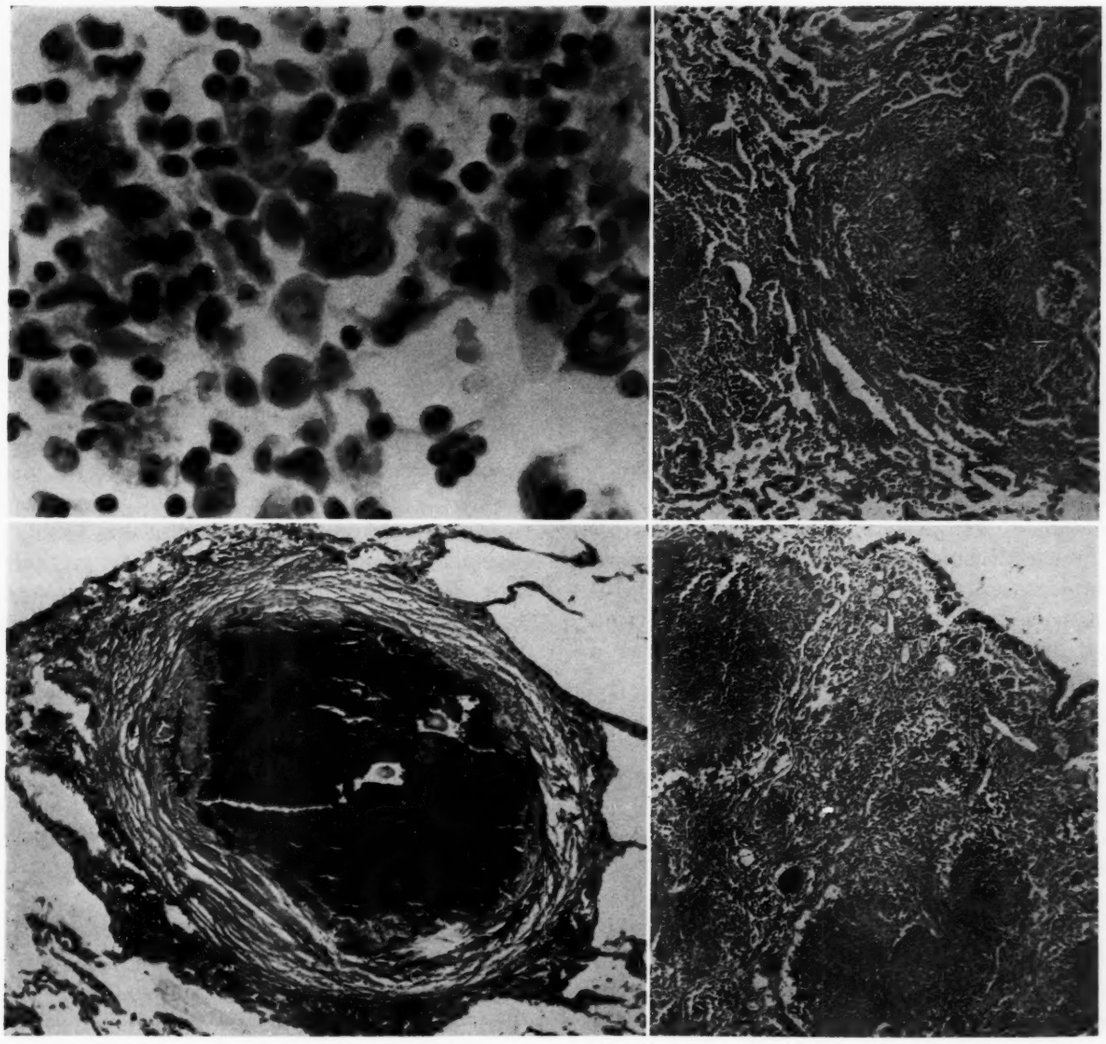


FIG. 7. Huge phagocytes filled with organisms in lymph node. (Courtesy Dr. M. L. Furcolow, Kansas City.) Original magnification × 900. Compare with Figure 2.

FIG. 8. Exudative and productive lesions in the same field; pulmonary histoplasmosis; original magnification × 65. (Courtesy Dr. M. L. Furcolow, Kansas City.)

FIG. 9. Calcified focus in a case of proved histoplasmosis; original magnification × 650. (Courtesy Dr. M. L. Furcolow, Kansas City.)

FIG. 10. Exudative caseating bronchopneumonia in histoplasmosis; original magnification × 65. (Courtesy Dr. M. L. Furcolow, Kansas City.)

corresponds with amazing accuracy to the incidence of positive reactions to histoplasmin in the same community.[68] We have had opportunity to observe classic complexes in three human cases and in four dogs with spontaneous disease.[110b] The pulmonary focus presents itself as a rule in the form of a small, circumscribed, generally caseated subpleural lesion which is more frequently seen in the lower two-thirds of the pulmonary lobes than in the upper third. Frequently, the overlying pleura has a slight fibrinous reaction, or in older cases a small adhesion may form at this point. The regional lymph nodes are always hyperplastic but our experience has been that caseation is not so complete or universal in the regional lymph nodes as in tuberculosis. The lymph nodes are considerably enlarged and of rubbery consistency. Frequently the color is ochre and differs from the yellow caseation seen in tuberculosis. From x-ray examination and autopsy material we know that the pulmonary focus and the

caseated lymph nodes can calcify. (Fig. 9.) How fast this occurs and whether it occurs regularly is not known. The multiple calcified foci so typically seen in histoplasmosis belong to a much later developmental stage. The cases with dissemination obviously produce massive invasion of the blood stream and hundreds of tubercules are formed in the interstitium of the lung; if these are necrotic, they later become calcified.[10,21a,b,31b,d,50,57,63a,68b,c,70,81a,b,120,123,146b,153a,168,187,216a,216b] Occasionally more than one primary focus can be formed. In tuberculosis a dozen or more primary foci may occur; it is likely that this occurs also in histoplasmosis.[7,20] Healing and calcification can be very slow and in some cases may not occur even after years.[63a,140]

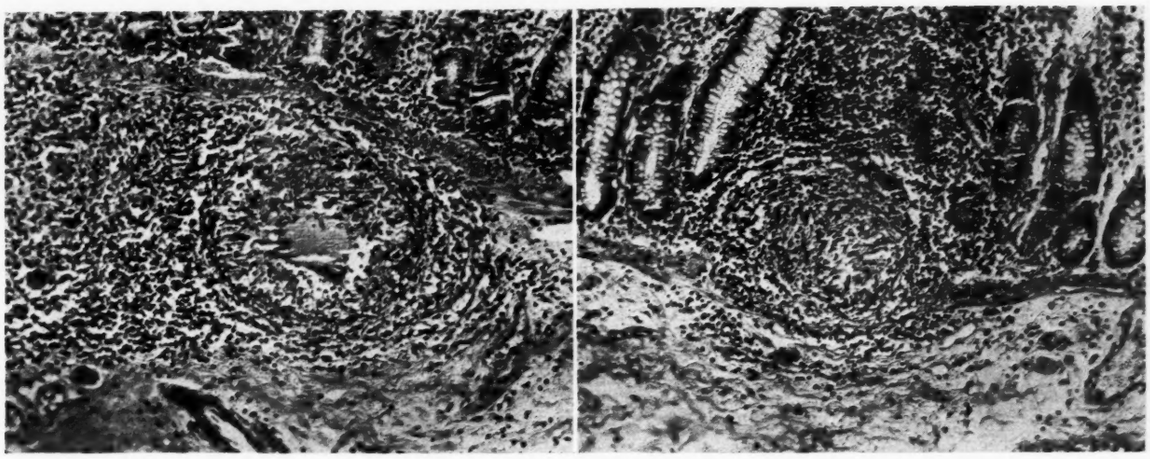
Evolution of Secondary Pulmonary Pathology. Lesions of histoplasmosis are seen in apical, subapical and other localizations; these may be coin-shaped and probably represent bronchogenic foci similar to the lesions observed in tuberculosis.[154,192] (Fig. 10.) The field of mycologic pathology is too young and too little material is available to permit more definitive statements. Whether these foci occasionally break down and are the source of cavity formation, or whether the cavities which are occasionally observed in histoplasmosis have a completely different origin is not known at present.[87,126,149] Occasional tumor-like (nodular) solitary lesions occur and offer an attractive field for surgery.[66,200,213] It is not known what the development of such solitary lesions would be if not treated. It is, however, well to remember that fungus diseases can have an extremely chronic course and the sequence of the developmental stages and allergic reactions is, at present, poorly understood.

While pleurisy may occur in any of the pneumonic involvements, it is seldom a predominant symptom clinically. In autopsy cases one can see the costal and visceral pleura studded with tubercles of a few millimeters in diameter, quite indistinguishable from the lesions observed in tuberculosis. Every known variety of exudate, including pus, has been found in the pleural cavity in selected cases of histoplasmosis. Scalene node biopsy has been successfully used in the diagnosis of histoplasmosis.[97]

Liver. The liver shows outstanding and very constant involvement in histoplasmosis, a fact which should be well considered for diagnostic reasons (liver biopsy)[4,13,180b] and for the prognostic outlook. The liver can become involved either by way of the hepatic artery or the portal vein, and, exceptionally (so far not reported), by umbilical veins or ascending from the duodenum via the bile duct (not reported). The most common source of infection of the liver, if there is bowel involvement, is probably through the portal vein. The hepatic phagocytes can become loaded to a degree which unquestionably must interfere not only with the specific functions of the reticulo-endothelial system in this organ but, by compression, also with the other functions of the liver. Sometimes we have seen sinusoids greatly distended and packed with swollen histiocytes; if the accumulation becomes very large, central necrosis may ensue. Less frequent than the histiocytic response is tubercle formation in the interstitium. One may find either very small foci of a few epitheloid cells with beginning central necrosis, or confluent or isolated well formed tubercles with occasional giant cells of the Langhans type. In overwhelming infection organisms may be found within liver cells or free in the capillaries and sinusoids. In addition to the more "specific" reaction there is frequently also cellular infiltrate, mostly of round cells, which sometimes can be quite prominent. Occasional histiocytes in the cellular exudate reveal the true nature of the inflammation.

Spleen. Splenomegaly, more often found in infants than in adults, is caused by hyperplasia of histiocytes which may be distended by numerous organisms. It is not unusual to see atrophy of the follicles and increase of the lymphocytes in the pulp. The capsule sometimes shows inflammatory reaction with fibrinous membranes which later become organized and fibrous. Tubercles, sometimes confluent and with caseation, are found in disseminated cases in combination with the histiocytic proliferation or as solitary lesions. One can only speculate why the spleen in infants is constantly enlarged, whereas in adults the enlargement is far less constant and less prominent. Since we do not yet know the role of reinfection, perhaps the answer will be found in the different pathogenetic development of disease in children as opposed to that in adults.

Adrenals. A rather specific and almost constant site of involvement is the adrenal glands.[200] A single organ or both organs may be attacked and any degree of involvement, from occasional small tubercles to massive and complete casea-



11 12

FIG. 11. Histoplasma "tubercle" in submucosa of large bowel, obviously of hematic origin; original magnification × 160. (Courtesy Dr. M. L. Furcolow, Kansas City.)

FIG. 12. Epithelioid cell nodule between mucosa and submucosa breaking through muscularis mucosa of large bowel; original magnification × 160. (Courtesy Dr. M. L. Furcolow, Kansas City.)

tion, is observed. The high incidence of involvement of the adrenals suggests some chemotactic mechanism. Histoplasmosis must be the cause of Addisonian symptomatology, especially in endemic areas where the prevalence of histoplasmosis infection is so much higher than tuberculosis in younger persons.

Intestine. Grossly the intestinal lesions are often very prominent both in number and in size. They represent either ulcerations of various sizes or infiltrates which can become quite polypoid and indurated. On the tips of such infiltrates small foci of necrosis or ulceration may develop. The regional lymph nodes can be found severely swollen and with foci of necrosis and even liquefaction. (Fig. 21.) On the other hand, intestinal lesions without marked regional lymphadenitis have been observed. Microscopically, one sees, as might be expected, enormous numbers of histiocytes loaded with innumerable organisms. Very frequently tuberculoid structures are formed but the location is often in the submucosa, indicating that at least two forms of intestinal involvement occur, that is, infection of the mucosa by deglutition and hematogenous spread to the submucosa with secondary breakdown of the tubercles toward the mucosa and formation of ulcers. (Figs. 11 and 12.) The lung is the main portal of entry but the occurrence of occasional primary intestinal infections cannot be denied, although they must be very exceptional. Again the similarity to tuberculosis, both in the pathogenesis and the morphologic character of the lesions, is obvious.

Bone Marrow. The bone marrow shows frequent involvement of a type which essentially follows the pattern described in the liver. Either there is a more or less diffuse proliferation of phagocytic elements which are distended by numerous organisms, or tubercle formation occurs.[152,166a,179] For further discussion, see the section on hematology.

Other Organs. Ulcerative lesions in the nasopharyngeal cavities are seen frequently in adults but are seldom observed in children. Perforating ulcers of the nasal septum have been described repeatedly and ulcerative lesions around the tonsils and even in the larynx are not unusual. It seems quite obvious that these lesions are not primary in nature since no regional lymph nodes are found, and it again becomes a matter of speculation as to why this localization should be so much more frequent in adults.

Any organ may be involved in generalized cases, including the heart, skin, central nervous system[49,178b] (Fig. 13), endocrine organs and bone (seldom).[46,54,101] References are given to papers dealing in somewhat more than casuistic form with localizations in specific organs or systems: mucocutaneous histoplasmosis;[41b,132,139b,145,195b] oral and nasopharyngeal involvement;[69,113b,135b,190,203,214] ocular;[44,107] adrenal disease;[158,195b,195b,200] splenic calcification in relation to skin sensitivity;[81,180e,216a,216b] gastrointestinal histoplasmosis and regional ileitis;[65,80,112,136,186,204a] heart;[11a,17,62] larynx[14,45,69,88,205] and urogenital disease.[41] Subendothelial proliferation has been recently described[2,11b,64] and the possibility of

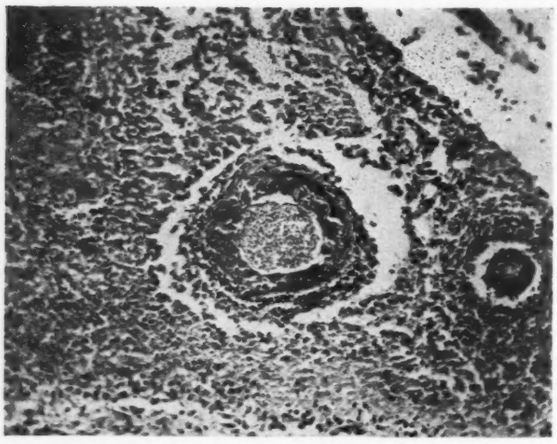


FIG. 13. Necrosis of vessel walls in meningitis in a patient with histoplasmosis. The morphology is practically identical with lesions seen in tuberculous meningitis and has all the implications of allergic reaction in reference to vascular necrosis. Original magnification × 160. (Courtesy Dr. M. L. Furcolow, Kansas City.)

focal necrosis secondary to vascular occlusion through bulging masses of subendothelial histiocytes is to be considered. Combinations with lymphomas[29,59,138] and sarcoid[23,93a,93b,151b,162] are discussed elsewhere and coincidental infections with B. dermatitidis,[111] C. neoformans[131,165,200] and M. tuberculosis[87,134,65] are on record.

HISTOPLASMOSIS AND LYMPHOMA

The coincidence of histoplasmosis with certain diseases of unknown etiology (lymphoma, sarcoid) has given rise to speculation whether the observations were purely accidental or a causal relationship existed. The combination of Hodgkin's disease[29,59,68c,63a,98,138,165] with histoplasmosis has been repeatedly reported. The authors had an opportunity to see slides from several of the cases and fully agree with the diagnosis based on morphologic grounds. Similar coincidental observations in leukemia have been reported.[110a,206]

Five main possibilities exist. (1) Coincidence: Statistically, two relatively rare diseases should not be found coexisting so frequently. (2) Malignant lymphoma predisposing to fungus infection: In view of the frequency with which other fungi (cryptococcus) also are found in malignant lymphoma, the possibility of predisposition due for instance to damage to the reticuloendothelial system by lymphoma, cannot be lightly dismissed. (3) Fungus infection predisposing to lymphoma: No evidence to support this view can be given at present. (4) The fungus actually causes histologic pictures similar or identical to what has been classified as lymphoma: No proof is available at this time. (5) Intensified search in lymphoma or sarcoid for organisms may give a higher number of positive reactions compared with more easily diagnosed tissue lesions; this is not very likely.

Very similar is the situation with respect to sarcoid where coexistence has been noted by competent observers.[93a,151b,160] Since at the present time the criteria for the diagnosis of lymphomas and sarcoid are mainly morphologic, the mutual relationship between these diseases and H. capsulatum is purely speculative.

HEMATOLOGY

In the numerous reports on the clinical features and laboratory findings in histoplasmosis, frequent mention is made of hematologic abnormalities that may occur to aid in the correct diagnosis. Chief among these is anemia, occurring either alone or in conjunction with leukopenia. The majority of the patients in whom hematologic data are available have had disseminated histoplasmosis so that knowledge of the alterations of the peripheral blood in the asymptomatic and non-fatal forms of the disease is relatively incomplete. Even in that form of disease which terminates fatally there is no "typical pattern" of hematologic change; normal results may be obtained[147b] and other hematologic entities simulated.[166b]

An attempt will be made to summarize the hematologic changes noted in different stages of infection with H. capsulatum as garnered from a review of reports in which sufficient data have been recorded. For details of observations made on patients reported up to January, 1945, the reader is referred to the review by Parsons and Zarafonetis[147b] in which blood counts are tabulated for approximately fifty patients. On the basis of this information and that obtained from material published since then[30,31c,59,62,64,83b,90,91a,91b,102,106a,122,138,141,144,152,165,166b,207] the following analysis has been made. Observations made on patients with proved histoplasmosis from the Children's Hospital are summarized in Table 1.

In this table representative blood counts are listed for those patients in whom multiple determinations were made. These were selected, insofar as was possible, before any form of therapy had been administered. Two patients exhibited rather marked fluctuations in total

white count. One of these is reported in detail herein (Case II, M. S.). In another patient (G. D. G.), previously reported by Christie,[31c] a diagnosis of visceral ascariasis or the Zuelzer-Apt syndrome might well have been suspected since at one time fever and hepatomegaly were present and a 32,150 white count with 36 per cent eosinophils was noted on differential smear. A liver biopsy at that time failed to reveal H. capsulatum but was also unlike the necrotizing granulomatous lesions seen in the Zuelzer-Apt syndrome. Six weeks later examination of the patient revealed the hematologic findings listed in Table I, at which time H. capsulatum was cultured from the marrow.

TABLE I

SUMMARY OF HEMATOLOGIC DATA ON ELEVEN CHILDREN WITH PROVED HISTOPLASMOSIS

Case	Age (yr.) and Sex	R.B.C. (mil./mm³)	Hbg. (gm. %)	V.P.R.C.* (ml./100 ml.)	Reticulocytes (%)	Platelets (per mm³)	W.B.C. (per mm³)	Differential				N.B.† per 100 W.B.C.	Marrow	
								P.M.N.	Lym.	Eos.	Mono.		Smear	Culture
C. S.	1, F	2.84	5.3	21	3.0	5,600	4,100	78	20	2	0	40	+	+
M. S.	4, F	3.94	8.2	28	2.2	230,000	9,100	71	23	1	5	0	−	+
B. S.	3, F	....	10.8	..	...	.....	14,400	..	..	..	..	..	−	+
B. J. P.‡	3½, F	2.9	7.9	..	2.7	80,000	13,100	75	14	..	11	0	+	+
G. D. G.‡	3 mo., M	4.14	8.8	33	...	80,000	6,100	29	53	..	18	3	−	+
M. C.§	2 mo., F	2.92	8.1	26	4.9	.....	4,700	41	47	..	12	2	−	+
R. P.§	11 mo., M	3.67	7.7	..	...	30,000	3,900	52	40	4	4	8	+	+
L. O.§	5 mo., F	2.91	6.1	..	3.6	110,000	1,200	58	42	..	..	1	+	¶
B. L. S.§	3 mo., F	2.72	7.1	..	...	.....	5,350	82	16	..	2	1	¶	¶
H. L.§	8 mo., M	3.8	8.1	..	...	110,000	2,150	52	38	8	2	16	−	¶
A. R. S.§	14, F	3.42	8.8	29	...	370,000	18,450	81	11	5	3	0	¶	¶

* V.P.R.C. indicates volume of packed red cells.
† N.B. indicates normoblasts.
‡ Previously reported by Christie.[31c]
§ Previously reported by Little.[114]
¶ Not done.

The pathogenesis of the hematologic changes noted is poorly understood. That there may be no single explanation for the frequently occurring anemia is obvious. Blood loss may be a factor in this disease, in which ulcerative intestinal lesions are found. Accelerated erythrocyte destruction, which occurs in various infections, may be an additional factor although there is no proof of its occurrence in histoplasmosis. Overt hemolysis seems likely, too, in view of the rapidity of recurrence of anemia in some patients despite transfusions and in the absence of obvious external blood loss. A microcytic hypochromic anemia in an infant found to have the disease may well be the result of preexistent nutritional deficiency of iron rather than a direct result of histoplasmosis itself. In certain instances the hematologic changes are identical with those seen in myelophthisic anemia and may then result from impaired function of the bone marrow organ secondary to overgrowth of parasitized reticuloendothelial cells. That the hematologic changes might also result from "secondary hypersplenism" or from suppression of bone marrow by a toxin liberated by the fungus is quite possible; however, there appears to be no satisfactory correlation between the size of the spleen and the degree of hematologic change, and the results of splenectomy have not been impressive.[5,144] Unfortunately, detailed hematologic studies in experimentally induced histoplasmosis in animals are lacking.

The anemia, which is usually of moderate severity but may be quite marked, occurs in approximately 75 per cent of patients with disseminated disease and in about one-third of those with local or non-disseminated histoplasmosis. Hemoglobin levels of 5 to 7 gm. per cent are rather commonly found in infants but are seldom so low in adults.

The size and hemoglobin concentration of red cells have not been sufficiently well studied to justify characterization of the anemia as normo-

cytic, normochromic, and so on. In two of the patients herein reported (C. S. and M. S.) the red cell indices indicated the presence of a microcytic, hypochromic anemia (mean corpuscular volume 71 and 74, mean corpuscular hemoglobin 18 and 21, mean corpuscular hemoglobin concentration 25 and 29). In one other (G. D. G.) previously reported[31c] but included in Table I the anemia was also microcytic and hypochromic. That this might occur often is not surprising in a disease which may be accompanied by ulcerative intestinal lesions and which has been reported rather frequently in infants and young children in whom iron deficiency anemia is so common.

Signs of active blood regeneration in the form of reticulocytosis, normoblastemia or alterations of red cell morphology are infrequently mentioned. A slight reticulocytosis (2 to 5 per cent) has been a frequent finding in children seen by the authors and has been recorded by others as well; in one instance it was as high as 48 per cent,[144] and this in an adult. Normoblasts in the peripheral blood would not seem to be a frequent finding in the cases reported, yet again from 1 to as many as 40 normoblasts/100 white cells have been noted in over half of our pediatric patients.

Polychromatophilia, aniso- and poikilocytosis and basophilic stippling have only occasionally been observed.

Leukopenia occurs at some time during disseminated histoplasmosis in from 50 to 60 per cent of patients. In half of these the white count is below 3,000, with counts as low as 800 reported.[31c] About one-third of those with nondisseminated forms of the disease develop leukopenia, which may be as severe as in widespread infections. There appears to be no correlation between leukopenia and either duration of illness or degree of splenomegaly. The leukopenia may be due to neutropenia but this is by no means invariable.

Leukocytosis is uncommon in the disseminated type of disease but occurs in at least one-third of those with clinical features which indicate localization of the infection to a single organ or organ system, for example, tongue, pulmonary system and so on. It appears to occur somewhat more often when lymphadenopathy is prominent. Leukemoid reactions may occur and marked fluctuations in the white count may develop from day to day (Case II, M. S.).

The differential white cell count is subject to wide variation and certainly exhibits no typical pattern. The percentage of granulocytes varies from very low to very high levels and there may be a distinct "shift to the left." Toxic granulation and other qualitative changes in the neutrophils have occasionally been noted. In a few instances monocytosis has developed. Eosinophilia is not prominent but isolated instances[90] of a marked increase in the percentage of eosinophils are recorded, as previously mentioned.

While histoplasmosis was first diagnosed during life by finding the fungus in circulating monocytes,[49] the organisms have since been found in peripheral blood smears in less than a dozen reported instances and then usually when the patient is in the terminal stages of the disease. Parasites may be found in neutrophils as well as monocytes. Kotcher[106a] called attention to the fact that demonstration of the fungi in peripheral blood is aided by making smears from the buffy coat. In two of the new cases reported herein, histoplasma were found in routine preparations of the peripheral blood in Case I and in stained smears of the buffy coat in Case III. It was more common to find a single organism engulfed but 3 to 4 fungi were often encountered and as many as 17 per neutrophils were found on one occasion. No special staining technics are required; routine Wright stain has been satisfactory in our work.

There are no studies available that help to clarify the etiology of the hemorrhagic tendency which has occasionally been encountered in disseminated histoplasmosis.[106a,114] Thrombocytopenia might, of course, contribute but has been recorded infrequently. Apparently, though, platelet counts have seldom been done. A moderate to marked thrombocytopenia occurred in almost half of our pediatric patients. (Table I.) One of the patients (Case R. P.) previously reported by Little[114] exhibited a marked tendency to hemorrhage in the terminal stages and was noted to have incoagulable blood in addition to thrombocytopenia and prolonged plasma prothrombin time. Another patient, herein reported (Case I), bled profusely for several hours prior to death. A marked thrombocytopenia was found but other studies designed to elucidate the defective homeostasis were not carried out. It is quite likely that the hemostatic defect is complex, such as occurs in parenchymal disease of the liver. The total serum protein in the patient R. P. referred to was in fact only 2.9 gm./100 cc.

Just as careful study of the peripheral blood may provide a clue to the correct diagnosis of histoplasmosis, morphologic study of the bone marrow may be diagnostic and its value definitely enhanced by simultaneous culture. Thus in one of the patients herein reported (M. S.) who was known to have widely disseminated disease, thorough examination of marrow smears at intervals during a protracted illness failed to reveal the fungi while marrow cultures for the organism almost invariably gave positive results. Of the nine patients in whom marrow examinations were performed (Table 1), histoplasma were found in the smears of four. In an additional four patients the culture gave positive results while the smear gave negative results.

There is a difference of opinion regarding the value of routine bone marrow cultures for H. capsulatum.[166a,179] Our experience would lead us to agree with Rohn[166a] that culture is of very definite value, especially in children. It was the single procedure establishing the diagnosis in a patient whose symptoms were minimal and not suspicious for histoplasmosis (Case v).

Detailed studies of the bone marrow in histoplasmosis, with differential cell counts, have not been reported. Usually one finds only statements regarding the presence or absence of organisms. Otherwise only gross estimates of cytologic changes are noted. Specimens are often said to be hypercellular and there may be increased numbers of macrophages; the latter may contain the fungi. As in the peripheral blood, however, H. capsulatum may be found in monocytes, neutrophils or plasma cells[166a] or may occur free in the marrow. There may be myeloid or erythroid hyperplasia and the number of plasma cells may be increased. Megaloblasts have been noted by two authors.[152,215] One adult patient may have had pernicious anemia.[152] However, the finding of megaloblasts in the bone marrow of infants with histoplasmosis, such as occurs in other disease states, is understandable and was in fact the case in two of the new patients reported herein (C. S. and M. S.). In one of these (M. S.) no reticulocytosis or alteration of the morphology of the marrow following folic acid therapy was noted. The morphology of the megakaryocytes had been inadequately studied. Provided parasites are not found, there seems to be nothing distinctive about the bone marrow in histoplasmosis.

Granted that there are obvious deficiencies in our knowledge of hematologic changes occurring in infections with H. capsulatum, it may be concluded that in an endemic region and in a patient with fever, respiratory symptoms and hepatosplenomegaly, the occurrence of anemia and leukopenia with or without thrombocytopenia is strongly suggestive of disseminated histoplasmosis. The presence of leukocytosis, however, should not deter one from suspecting the disease. Careful examination of the buffy coat from peripheral blood and of marrow may be diagnostic, and culture of the marrow and blood can certainly be recommended.

SEX INCIDENCE

There is a significant sex difference of proved disease in adults, males outnumbering females about four to one.[178a] In children the frequency is approximately equal in the two sexes. A decrease in the incidence of skin sensitivity to histoplasmin has been noted in females at the end of the second decade.[68h] The difference between sexes has been considered a possible expression of social patterns which limit exposure to infection but biologic factors cannot be excluded. No significant racial differences have been recognized.

CLINICAL FEATURES

The clinical manifestations of histoplasmosis can be derived from the many reports now available. Mochi and Edwards[133] in 1951 were able to assemble 370 papers dealing with clinical reports of histoplasmosis and with results of histoplasmin skin testing in various parts of the world. Proved cases have been described with signs and symptoms related to practically every body organ and system. However, when many of the reports are reviewed critically assurance that the disease causing the signs and symptoms is indeed histoplasmosis is often lacking. Diagnoses based on positive skin sensitivity, on roentgen observation, on the more recently developed immunologic procedures and even on microscopic studies of tissues removed at biopsy or necropsy can in many instances be discarded as inconclusive or grossly erroneous. This does not mean that the technics are valueless or that cultural technics alone are satisfactory; it does mean that every available method of diagnosis should be exploited in cases in which the disease is suspected and that the

criteria for suspecting the disease should be derived from those reports which withstand critical scrutiny.

It is generally agreed that there is a clinical disease spectrum of infection with H. capsulatum which extends from no apparent illness to fulminating fatal disease. For purposes of discussion, three broad classifications can be considered to bridge this spectrum. Considerable overlapping occurs in successive portions of the classification.

1. Fatal, Symptomatic Histoplasmosis. In children the fatal form of the disseminated disease is commonly characterized by fever, anemia, weakness and hepatosplenomegaly. The review by Iams and associates[91b] describes the clinical manifestations in great detail. The signs and symptoms depend in part on the degree of systemic involvement, in part on the extent to which individual organs are affected. "Toxicity" *per se* does not adequately account for fever which has been practically a universal observation. Widespread infection has been noted in children with little or no temperature elevation. It appears likely that the febrile reaction represents a response to secondary infection by bacteria capable of more pyrogenic activity than the fungus. Absorption of "toxic" breakdown products from necrotized parasitized cells may be related to the fever in the absence of secondary infection. No characteristic type of febrile reaction has been noted; hyperpyrexia is a not infrequent terminal event after a progressive septic type of fever. Prolonged or increasing pyrexia is an ominous sign.

Anemia of moderate to severe degree is usually present. The number of white blood cells in the peripheral blood tends to be depressed although occasionally leukocytosis is observed. A leukemoid reaction has been observed on many occasions and clinical and hematologic confusion with leukemia has been noted. Careful evaluation of young children or infants considered to have leukemia, who give a history of having siblings who died of similar complaints, may be very productive in the discovery of additional cases of disseminated histoplasmosis. Further discussion of the hematologic aspects of histoplasmosis is included in the section on hematology.

In adults, particularly the very old, the clinical course is not dissimilar. Frequently, histoplasmosis occurs as a complication of other serious, more or less chronic diseases. The association with Hodgkin's disease and sarcoid is commented on elsewhere in this paper. Pulmonary manifestations are more common in adults, as are localized ulcers of the mucous membranes of the upper alimentary or respiratory tracts. The course is like that of an overwhelming septicemia with rapid progression. A variant seen in adults is the chronic progressive form. This may persist for years, usually with extensive pulmonary involvement associated with cavitation and progressive change. In many respects this resembles chronic tuberculosis and sometimes is associated with it.

2. Non-fatal, Symptomatic Histoplasmosis. This group may be divided into mild, moderate and severe forms and does not differ appreciably in children and adults. Influenza-like symptoms are common with prominent respiratory manifestations. The onset is often sudden with cough and chest pain. Temperature elevation is commensurate with the general severity of illness. The diagnosis of atypical pneumonia is commonly made. Infants may have a clinical course indistinguishable from that of the fatal cases except for the final outcome, and recovery may ensue without relation to attempted therapy. In many of these patients intrathoracic calcification was demonstrated in roentgenograms following recovery. The variable degrees of illness are well illustrated in those cases included in the reports of "epidemics."[60,68f,72c,116a,119] Local lesions in individual organs occur; symptoms are then related to the site of disease.

3. Non-fatal, Asymptomatic Histoplasmosis. The largest number of case reports is found in relation to this and the preceding classification, and the proof of diagnosis is often equivocal. The increasing number of unequivocal cases, however, tends to support the validity of the diagnosis in the previous cases. Most of the information comes from epidemiologic studies in relation to histoplasmin sensitivity and pulmonary calcification. Calcification elsewhere in the body (spleen) also is significantly more frequent in geographic areas with high histoplasmin sensitivity rates than in areas of low sensitivity rates. Careful search, specifically directed toward the recognition of H. capsulatum in patients dying of other conditions adequate to explain symptoms, is proving productive.[31a] Comparable success is promised by biopsy technics. Study of serial chest roentgenograms in children who are known to have given positive reactions to histoplasmin and to have developed humoral antibodies have revealed pulmonary lesions in

asymptomatic children who subsequently develop intrathoracic calcification. It may be that the designation "asymptomatic" represents limitations of clinical diagnosis as currently practiced and that the better designation would be "inapparent infection." To any physician aware of histoplasmosis it is obvious that any of the "colds," "upset stomachs," or other benign conditions which rarely demand professional medical attention may actually represent the symptoms of initial infection with H. capsulatum.

From epidemiologic studies[72c] the incubation period of the disease is estimated as from five to fifteen days. Even with this information the case reported by Schlumberger and Service[175] of an infant dying of the disseminated disease at the age of nine and a half weeks raises the question of intrauterine infection. The infant spent two weeks in the hospital because of premature birth (eight months' gestation, birth weight 5 pounds), was home for four weeks and was admitted to the hospital in the seventh week with hepatosplenomegaly, pallor and signs of widespread infection.

A consideration of signs and symptoms in the various organ systems permits an appreciation of the protean nature of histoplasmosis. Because one classification merges so imperceptibly into the next, no attempt will be made to specify which of the signs or symptoms are related to any of our arbitrary groups. To do so would be to admit a prognostic implication which does not exist.

Respiratory System. This is probably the portal of entry in the majority of cases. In a statistical study of the frequency of occurrence of the lesions of histoplasmosis, Schulz[178a] found the lungs to be most frequently involved in children over five years of age and in adults, whereas liver and lymph nodes exceeded lungs in frequency of lesions in children under five years of age. These figures were derived from autopsied patients only and therefore probably do not reflect what clinical experience would maintain, namely, that respiratory involvement must occur in almost 100 per cent of patients. Pulmonary symptoms are reviewed in detail in the papers by Hodgson et al.[83b] and Schwartz.[179a] Cough is not uncommon. It is generally non-productive, unless there is associated cavitation. It may be associated with chest pain. Hemoptysis is rare; the expectoration of broncholiths has been described in an unproved case.[94] Some patients have demonstrated dyspnea. Night sweats have been present in occasional cases. Physical signs vary with the degree of lung involvement, as in any other infection, but more frequently than not they are totally lacking. Atelectasis, emphysema, cavitation, and so on, produce the same signs as when caused by other agents.[12,83b,96]

In adults, granulomatous lesions of the upper respiratory passages have occurred with considerable frequency. Nasal and laryngeal ulcerations of a chronic nature are repeatedly described. Hoarseness is noted as the presenting symptom in many cases.[88,199a] The lack of response of symptoms to treatment with streptomycin within one week has been considered by Hulse[88] as a means of differentiating laryngeal histoplasmosis from laryngeal tuberculosis. Pleural effusion from which organisms have been cultured has been described[6,54,78] (Case III). The diagnosis has been made by biopsy of a scalene lymph node in the fashion which has been helpful in the diagnosis of sarcoid and cancer.[97]

Gastrointestinal System. Ulcerating, granulomatous lesions of the oropharynx[41b,203] and of the perianal region[145,204a] occur in both fatal and non-fatal cases. All intervening anatomic divisions of the gastrointestinal tract have been implicated. Weakness, sore throat and dysphagia accompany lesions in the oral cavity. These lesions often spread to the upper respiratory passages. Gastric ulcer with massive hemorrhage has been described.[65] Ulcerative enteritis has been found at all levels; the clinical manifestations of such involvement, apart from the anorexia which may be systemic rather than local in origin, have been largely diarrhea and/or melena.[64,80] Icterus has been reported in some cases but is not common; hypoproteinemic edema may occur, related in part to involvement of the liver. Hypergammaglobulinemia may occur (Case II). Hepatosplenomegaly has been the hallmark of the disease in the disseminated fatal form in infants. Histoplasmosis is very likely to be the correct diagnosis in a pale, febrile child with marked hepatosplenomegaly in the endemic area. Abdominal enlargement is a common observation in infants; in adults the enlarged organs are frequently palpated but abdominal enlargement is rare. Intra-abdominal masses of lymph nodes are occasionally palpated.

Genitourinary System. Although involvement of practically all organs of this system has been observed histologically, clinical signs are largely restricted to penile, chancre-like lesions in adults[41b] and manifestations of adrenal insuffi-

ciency in all ages.[160] Classical Addison's disease has been noted in several fatal cases in adults, and histologic involvement of the adrenal is so frequent as to make histoplasmosis suspect whenever signs of Addison's disease are observed in the endemic area. No proved transplacental cases are recorded but the early age of clinical onset in some cases[175] has raised this possibility.

Cardiovascular System. Endocardial lesions have been noted at autopsy in several instances.[11a,17,19] In one case[68c] there was electrocardiographic evidence of right bundle branch block but this was not necessarily related to the local cardiac lesions present. Periarteritis has been reported;[27] subendothelial masses of parasitized macrophages[178a] might be expected to be associated with other vascular lesions.

Nervous System. The fact that lesions have been found in the brain[99] raises the interesting possibility that some of the convulsive episodes, periods of coma, and so on, may be related to local brain disease. Clear-cut localizing neurologic signs related to a distinct lesion of the central nervous system have not been recognized. Chorioretinitis may be considered a manifestation of nervous system involvement. One patient with a positive complement fixation test had clinical chorioretinitis supposedly "reactivated" by the application of a skin test which gave strong positive results.[107]

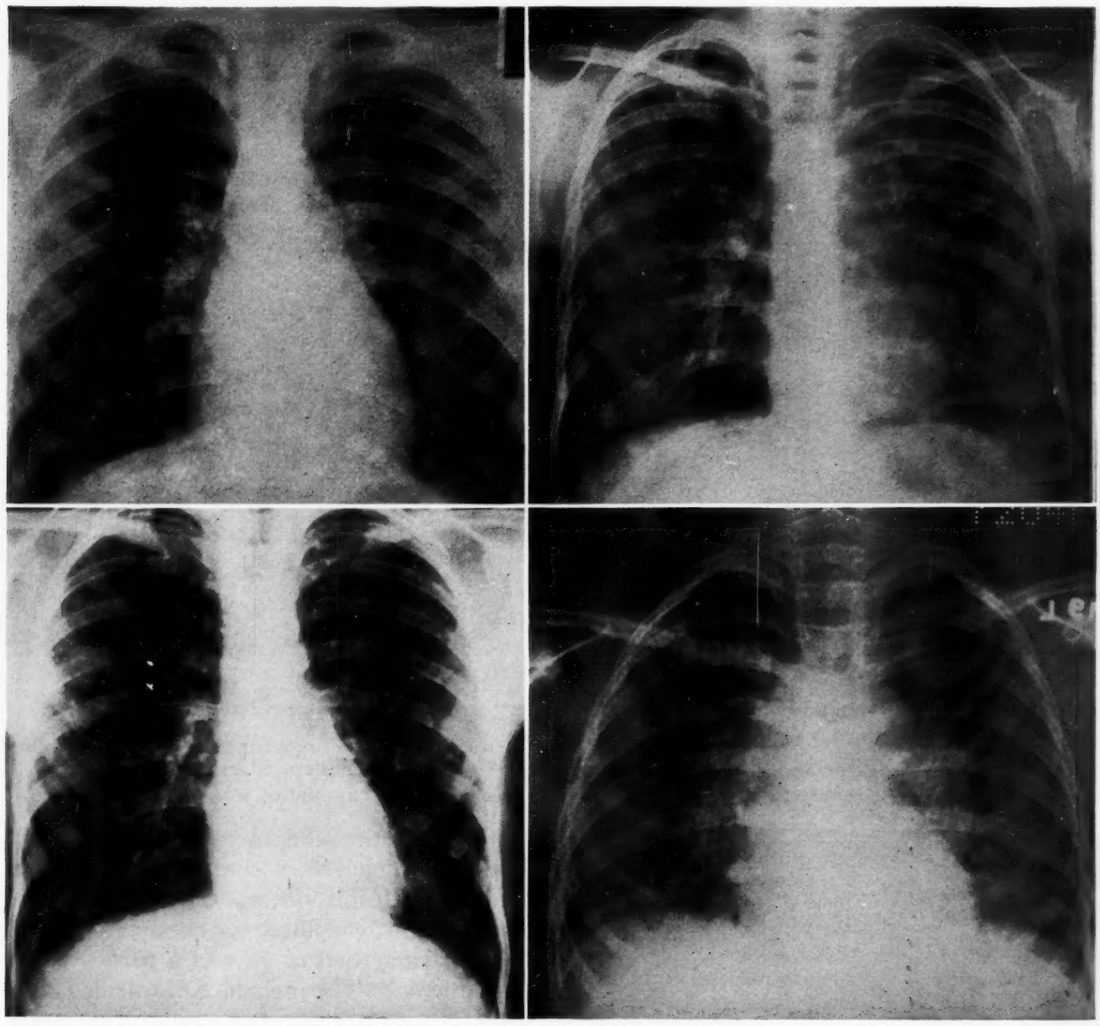
Eyes and Ears. Apart from the chorioretinitis noted, a high incidence of positive histoplasmin reactions has been observed in patients with uveitis.[44] The middle ear has been the site of histoplasmosal lesions; no diagnostic clinical features are described but the organism may be found in purulent aural discharge.[135b]

Skin. Skin nodules have been found in some cases and biopsy in such cases has established the diagnosis.[76,95,195b] In one of our cases exfoliative dermatitis was present, and following treatment with ACTH the skin became the site of intensive and extensive histoplasma proliferation. It is strange that erythema nodosum, which is common in coccidioidomycosis, has not been unequivocally present in histoplasmosis; in those cases wherein it is described either the lesions have not been typical or the possibility of another mechanism such as penicillin reaction exists.[68c,78] Rarely, granulomatous lesions develop at sites of excision of infected lymph nodes for biopsy purposes.[48] One of the authors' patients had an incision and drainage of a mass of necrotic cervical lymph nodes and, although healing was slow, it was complete.

Skeletal System. Key[101a] described clinical arthritis of the knee with osseous destruction leading to amputation. Organisms were found in the thickened synovia and in the granulation tissue of the bone. General skeletal involvement has been infrequently reported.[104,121] With the frequency of marrow involvement in the disseminated disease, however, lesions of bone must occur but are probably too small or diffuse for roentgen recognition. Infection in a sternoclavicular joint has been described[131] but apparently was associated with torula infection.

RADIOLOGIC FEATURES

Radiologic examination of the chest is one of the most important factors in calling attention to the frequency of histoplasmosis in certain areas of the country. Nevertheless, except for the recognition of disseminated intrathoracic calcifications (Figs. 14 and 15B), there are no diagnostic features which clearly differentiate radiologic signs of histoplasmosis from other pulmonary inflammatory disease. Claims for diagnostic specificity of "mulberry-like" calcifications or focal calcification with a "soft halo" do not stand critical scrutiny. Nodular foci of increased density, pneumonic infiltrations, hilar and mediastinal lymphadenopathy, disseminated infiltrates and various combinations have been observed during the acute phase of the disease.[68j, 85,187] (Figs. 15, 16 and 17.) The shadows tend to persist much as those of tuberculosis with which they are often confused. Atelectasis and emphysema of a lung or of a lobe may result from bronchial compression by involved lymph nodes. Many of the lesions go on to calcify, producing primary complexes which are indistinguishable from those of tuberculosis. (Fig. 18.) Calcification has been observed to develop in as short a time as four or five months after clinical illness.[108] Solitary lesions, "histoplasmomas," have been described and have been resected; it is not clear how certain the diagnosis of histoplasmosis was in some cases but morphologic and cultural proof has been offered in others.[126, 154] The presence or absence of calcification within the solitary lesions has no diagnostic significance. In some of the "epidemic" cases fine widespread reticulations are observed in the lungs (Fig. 17);[63a] calcification seems less common in this type of reaction than in the focal or nodular variety. Gross cavitation has



14 15A

15B 16

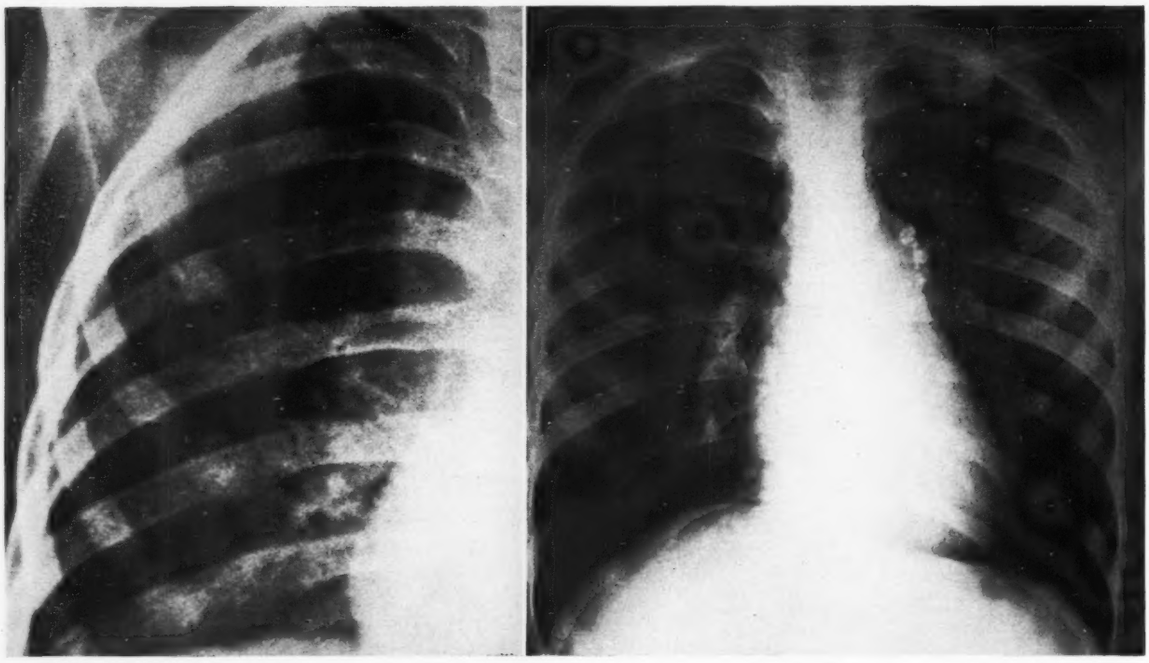
FIG. 14. Probable histoplasmosis; disseminated calcification in a boy who gave a negative reaction to tuberculin and a positive reaction to histoplasmin. No definite respiratory infection was present, yet lesions developed while the patient was under careful medical supervision for rheumatic fever. This roentgen picture is practically diagnostic of remote infection in the endemic area. (From *Am. J. Roentgenol.*, 64: 747, 1950.)

FIG. 15. A, probable histoplasmosis; acute respiratory illness; x-ray diagnosis of "miliary tuberculosis." Negative reaction to P.P.D., positive reaction to histoplasmin six months after acute episode following discharge from tuberculosis sanitarium where diagnosis of tuberculosis had been disproved. B, two and one-half years later; patient clinically well. Note beginning of disseminated calcification.

FIG. 16. Probable histoplasmosis; positive reaction to the skin test and C.F.R. This is an example of diffuse nodular pulmonary disease with hilar lymphadenomegaly. (From *Am. J. Roentgenol.*, 64: 747, 1950.)

been observed exclusively in adults, many of whom were under treatment for tuberculosis which they did not have. Others with cavitation have had both diseases, but radiologic features did not permit evaluation of the contributions provided by each separately. Pleural reactions are readily recognized roentgenographically when present.

The absence of pathologic pulmonary shadows does not exclude pulmonary involvement. The limitations of size of lesions, shape, sharpness of margins, location and total number which apply to any disease militate against roentgen recognition of disease in histoplasmosis as well. In Case 1 review of the chest film taken less than twenty-four hours before death failed to identify two well developed primary foci found on autopsy, each measuring 3 mm. in diameter and containing enough calcium to be gritty when sectioned. Although lesions are found in the thymus, enlargement of this organ due to histoplasmosis is seldom seen.[82]



17 18

FIG. 17. Proved fatal disseminated histoplasmosis in an infant; markings in the lung demonstrate a free reticular pattern; the interlobar pleura is slightly thickened.

FIG. 18. Case VII (B. J. S.); proved asymptomatic histoplasmosis. Calcifying lymph node removed during surgery for uncomplicated patency of the ductus arteriosus; many non-viable typical H. capsulatum were found. (See Fig. 37.)

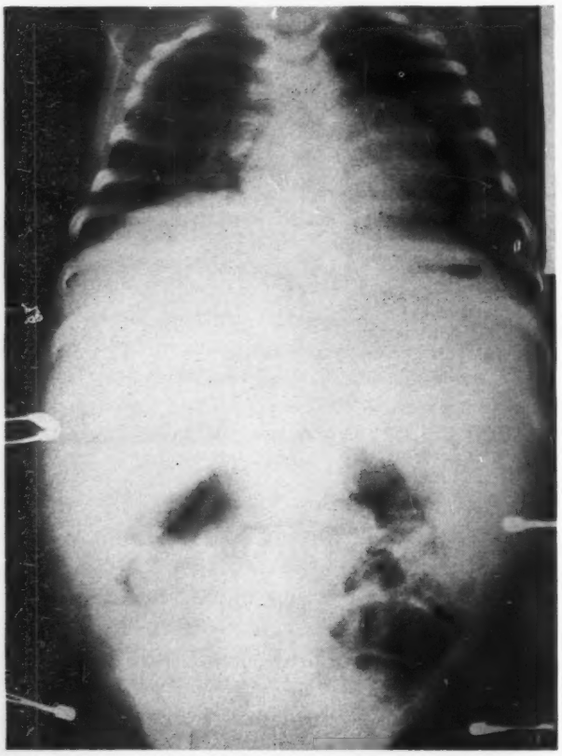


FIG. 19. Proved histoplasmosis with spontaneous recovery; note massive hepatosplenomegaly. (From *Am. J. Roentgenol.*, 64: 747, 1950.)

Films of the abdomen, or portions of the abdomen included in chest films, may demonstrate hepatosplenomegaly. (Fig. 19.) Splenic calcification was found in chest films in a few persons examined as part of a survey by High and others.[81a] The incidence of splenic calcification is not adequately portrayed by clinical roentgen examination of either the chest or the abdomen. In a study of spleens removed routinely at autopsy and radiographed, the incidence of splenic calcification in a region of high histoplasmin sensitivity rates is more than ten times that in a region where the disease is known to be practically non-existent.[180e] Other extrapulmonary calcification may occur, for example, in axillary lymph nodes, but thus far proof of infection in such cases is only circumstantial.

The bone lesion described by Key[101a] was merely spotty bone atrophy associated with soft tissue thickening about the knee and fluid in the joint. No productive changes were present. Granulation tissue with cells containing parasitized organisms was found to be invading the bone in the area where the demineralization was noted.

Radiologic examination of other body sys-

tems has not been reported as helpful. Undoubtedly, ulcerations of the gastrointestinal mucosa might be identified in some cases; perhaps contrast studies of the large bowel in those cases with colitis or of the small bowel in those with enteritis may prove of value.

DIAGNOSIS

The diagnosis of histoplasmosis must be based on the demonstration of organisms, with preference by culture. The indirect methods like complement fixation will only under very special circumstances replace a culture as acceptable proof. Frequently, especially in endemic areas, the decision as to whether or not a case can be classified as histoplasmosis may be very difficult in the absence of a positive culture.

The morphologic diagnosis of H. capsulatum in tissue can be accepted only seldom and only in the hands of experienced observers. The similarities with Histoplasma farciminosum and organisms of the leishmania group have been mentioned repeatedly. Furthermore, cell debris especially in lymph follicles is indistinguishable from isolated organisms, and in every appendix or tonsil structures can be found which resemble but cannot be proven to be organisms. Misinterpretation of such débris as histoplasma has been repeatedly reported.[156a,b,208]

Unfortunately, and for obvious reasons, it is hard to estimate how often organisms are missed. We have often searched unsuccessfully for histoplasma in proved cases for hours. We found little help from periodic acid stain in locating a small number of organisms; however, the Gridley procedure[73b] offers so much contrast that it contributes greatly to the search for fungi in tissues. On the other hand, observations like those of Raftery which report the organism in 5 per cent of random samples of appendices are open to question. His work has been checked by reliable observers and by cultural methods, and the presence of histoplasma in normal appendices has not been established.[32,169]

Histoplasmosis, as we see it, is a disease which is acquired by way of the respiratory tract almost without exception. As in most granulomatous diseases, an overwhelming majority of persons affected with the primary infection are asymptomatic and the episode is self-limited. The arrest of the primary infection is frequently permanent, and its recognition is often limited to radiographic demonstration of calcific chest lesions. Rarely, the disease can become progressive or reinfection may occur. It is not possible at our present level of information to say whether chronic, active (often cavitary) histoplasmosis is derived directly from the primary infection or whether it represents reinfection. If the latter, by analogy with well established facts in tuberculosis, endogenous or exogenous mechanisms could be involved. It seems fairly certain from the Cincinnati epidemic[170] that heavy exposure may produce exogenous reinfection; how often endogenous reinfection occurs is not known at present. The isolated tuberculoma-like lesions, which are found in the lungs with increasing frequency and which are being resected as "histoplasmomas," may represent foci of lymphatic, hematogenous or even bronchogenic reinfection. We have no knowledge of the effect on the disease of sensitization, nor of what mechanisms are responsible for encapsulation on the one hand or dissemination on the other. It would indeed be of paramount importance to obtain information on these points.

We recommend the following step-by-step procedure in a case of suspected histoplasmosis: (1) *Skin test.* If the results are positive, the possibility exists that the disease is histoplasmosis. Special care must be taken with respect to proper dilution, potency and sterility of the antigen. If the results are negative, the possibility of the presence of histoplasmosis is remote unless the patient is severely ill or in the incubation period. (2) *Complement fixation test.* The difficulty of obtaining a reliable test cannot be overestimated. A positive reaction to the test with high titer is generally indicative of progressive disease but cross reaction should be ruled out. Low titer or negative reactions do not rule out active disease. (3) *Biopsy* of enlarged lymph nodes, mucocutaneous lesions, liver, and so on. (4) *Culture from blood and bone marrow.* (5) *Culture of material from organs producing symptoms*, sputum or gastric washings, skin exudate, feces, urine (all contaminated material mixed with antibiotics should be injected into the peritoneal cavity of mice).

It cannot be overemphasized that the demonstration of the organism in blood smears, bone marrow, tissue, sputum, and other sources, requires skill which cannot be expected from every laboratory, especially outside the endemic area. This refers both to microscopic and cultural demonstration. The statement is borne out by the amazingly small number of cases which

would fulfill even modest minimal standards of diagnosis.

TREATMENT

It is quite obvious from the extreme variation in the clinical course of the disease that evaluation of any therapeutic agent must be extremely difficult. To date no specific therapy has been developed. Supportive treatment in the form of dietary measures, food supplements, transfusions, effective treatment for underlying or superimposed disease, is governed by considerations unrelated to the presence of histoplasmosis, and the indications are well known and clearly defined.

The rapidly progressive, disseminated cases of histoplasmosis seen especially in childhood (Case I) compare with the disseminated cases observed in tuberculosis as a consequence of primary infection at a time when body defenses have not been mobilized or have proved to be inadequate. Paradoxically, one would expect these cases to be most benefited by chemotherapy if and when such therapy becomes available. In the disseminated cases the problem would seem to be one of fungicidal therapy. The chronic cases may not need eradication of the organisms so much as a general change of the internal environment. The internal environment probably is altered initially by the fungus, becomes less important in the granulomatous forms of the disease, but assumes a significant role as in Cases III and IV when sensitization, perhaps, permits extensive proliferation of the organism.

Specific drugs which have been used in individual cases of histoplasmosis or evaluated *in vitro* include arsenicals, sulfonamides, iodides, organic fungicides, antimony compounds, antibiotics, and so on. Radiation therapy and surgical resection have been described.

Arsenicals. Various arsenical preparations have been tried since the earliest case reports. Reports of success in the treatment of epizootic farciminosis with arsenicals naturally led to its use in histoplasmosis, the causative organism of which may be closely related to H. farciminosum.[184] Seabury and Artis[182b] found neoarsphenamine effective against H. capsulatum *in vitro* in a concentration of 100 mg./100 cc. It is doubtful whether levels of this magnitude could be reached and maintained safely in tissue fluids.

Sulfonamides. The availability of these chemotherapeutic agents coincided with the recognition of histoplasmosis as a not so rare disease. Various members of this family have been used in individual cases or very small series with variable results.[41b] Sulfanilamide and sulfadiazine were thought by some to influence the disease but experimental studies would seem to indicate that these drugs in accepted dosage would not be effective.[113,182b]

Organic Fungicides. At least two preparations used to inhibit fungus growth in commercial enterprises (baking) have been given fairly intensive study. Christie[31c] reported treating twelve infants with the disseminated form of the disease with ethyl vanillate; five children recovered but the relationship between administration of the drug and the recovery is far from proved. Toxicity of this agent is great and, in general, further use of the drug in its present form is not recommended. Sodium propionate has been studied under experimental conditions;[113d] it does inhibit the growth of the organism but clinical success has not been reported.

Antimony Compounds. Certain clinical and pathologic similarities of histoplasmosis and kala-azar undoubtedly led to consideration of antimony compounds in the former disease by virtue of its long association with the latter. Fuadin® and neostam® have proved ineffective in *in vitro* studies.[89,113a,182b] H. capsulatum was susceptible to stilbamidine *in vitro* in concentrations between 10 to 100 mg./100 cc.[182b] but subsequent clinical trial was unsuccessful in influencing the course of the disease.[182a] Because of apparent success in the treatment of blastomycosis,[189] 2-hydroxystilbamidine has been offered as a possible antihistoplasmal agent.[182a] In one case (Case II) the drug was not clearly beneficial and may have been toxic. Meleney[127] mentions clinical remission during neostam treatment; other reports of the clinical use of antimony are not encouraging.

Antibiotics. None of the regularly available antibiotics has been found to affect H. capsulatum. In fact, through inhibition of various other microorganisms, these agents may actually enhance the invasive and pathogenetic properties of H. capsulatum.[182b,c] Experimental studies have identified at least one laboratory antibiotic which may have some effect. Fungicidin, obtained from a soil actinomycete by Hazen and Brown,[77a] is reported to be active against H. capsulatum *in vitro*, as well as against Candida albicans and others. This antibiotic, also known as nystatin,® has given promis-

ing results in experimental histoplasmosis in animals.[22e,52a,77c] Hulse[88] regarded the lack of response of laryngeal lesions to streptomycin as a test differentiating histoplasmosis from tuberculosis.

Miscellaneous. Atabrine® was found experimentally to inhibit the growth of H. capsulatum *in vitro*.[22d] Experimentally infected mice showed increasing survival rates with increasing dosage schedules. Organisms were present in the spleen of both treated and untreated mice, indicating that the effect of atabrine was suppressive rather than lethal. Treatment begun one week after infection was ineffective in reducing mortality rates. Hansen and Bean[75] found a abrine ineffective at concentrations which generally produced effects. Iodides were ineffective *in vitro*[113a] and had no clearly defined clinical effect.[118b,135b]

Radiation therapy has been used for some of the localized lesions[80,147b] and for splenomegaly.[20] Results have been equivocal; local lesions may respond. However, Brandt[16a] believed that radiation enhanced experimental infectivity in mice and warned against x-ray therapy in human disease. A comparable warning, resulting from a somewhat similar mechanism, may be read in Cases III and IV with regard to the use of cortisone. The apparent run-away spread of the disease in our two patients so treated may constitute an additional contraindication to indiscriminate use of such medication in an endemic area of histoplasmosis. Experimental histoplasmosis in mice did not, however, become disseminated after cortisone injections.[9]

Certain antihistaminics were found to exert an inhibitory effect on H. capsulatum, among other fungi, in experimental studies but effective concentrations are beyond the range of clinical usage.[24]

Surgical incision of local lesions might be expected to yield a cure in the absence of disease elsewhere in the body. Recent interest has been raised with respect to excision of pulmonary lesions.[12,83a,126,154,213] In tuberculosis, in which resection has become popular, chemotherapeutic and antibiotic auxiliaries are available; in the absence of such additional support in histoplasmosis considerable reserve must be maintained with regard to surgical therapy. Splenectomy has been reported in several cases.[5,20,144] The indication has generally been marked splenomegaly and "hypersplenism." Recovery and death have been reported but it is interesting to know that recovery can occur when hypersplenism is relieved. A report of improvement after administration of acti-dione® is available.[207] Negroni[139a] speaks of a vaccine but his report is open to considerable question.

Vaccination has been shown to be effective for short intervals in mice[171h,173] but a prophylactic program in humans does not seem feasible. The disease is one in which infected individuals seldom become obviously symptomatic so that evaluation of protection would be extremely difficult if not impossible. Moreover, repeated injections are necessary to maintain immunity, and no clear criteria are available for selection of any particular group as most desirable for vaccination. Most "natives" in the endemic areas apparently acquire the disease even at school age; their skin sensitivity may be related to natural immunity. Newcomers to the area might be considered at greater risk from histoplasmosis but it is clear that many adults who enter an endemic area remain permanently nonreactive to histoplasmin. Prevention of the disease is difficult to visualize if the concept of soil contamination and inhalation of dust proves to be correct. Menges' report[129g] of finding H. capsulatum in the soil while searching for blastomyces in a place where a dog was found with blastomycosis serves to illustrate how widespread is the contamination of soil in the endemic area.

Hansen and Beane[75] report no effective *in vitro* action by a variety of agents including certain chlorinated hydrocarbons, quinine, emetine, aminopterin, PASA and urethane. Currently, beta-di-ethylaminoethyl fencholate is under investigation.[117]

We are frequently confronted with the problem as to whether or not an individual with primary disease diagnosed by change in skin sensitivity and/or radiographic changes should be kept in bed. Likewise, the question of prolonged bed rest is encountered in cases of cavitary disease. Too little is known at present about the natural course of the disease to make any fast rules about the management of patients but it does seem reasonable to say that primary infection does not require bed rest once the acute febrile episode and respiratory symptoms have subsided. No cases of generalized disease have been traced to overexertion or overexposure. Chronic cavitary lesions probably require bed rest only as part of the general supportive therapy. Whether or not in the future surgical

procedures like pneumothorax, thoracoplasty, and so on, will be shown to be helpful in accelerating closure of cavities we do not dare prognosticate. Since no evidence has been presented that resection of isolated pulmonary lesions conclusively improved the prognosis in tuberculosis, it is obvious that resection of isolated pulmonary lesions in the less well studied histoplasmosis is far from an established therapeutic procedure. Naturally, surgery will be indicated and permitted in all cases in which the slightest doubt exists concerning diagnosis, and in which the possibility of malignant tumor must be considered. It may be an important consideration that no drugs are available at present to safeguard patients from extension of infection after surgery in histoplasmosis the way streptomycin and allied drugs provide an "umbrella of protection" in tuberculosis.

CASE REPORTS

CASE I. C. S., born December 30, 1950, was admitted to the hospital on December 16, 1952, because of a low-grade fever of insidious onset and loss of appetite of three weeks' duration, and a high fever for four days prior to admission. The patient did not respond to treatment with antibiotics.

The birth, development, feeding and past medical histories were non-contributory. The family history was interesting insofar as a female sibling was admitted to the hospital December 18, 1952, and subsequently proved to have disseminated histoplasmosis (Case II). Epidemiologic aspects will be the subject of another communication.[1]

Physical examination at the time of admission revealed a somewhat pale girl who appeared both acutely and chronically ill. The weight was 18 pounds, 4 ounces; temperature 103.4°F., pulse rate 160; respiration rate 100. Small cervical lymph nodes were present, the liver was easily palpable four fingerbreadths below the right costal margin and the spleen was easily palpable two and one-half fingerbreadths below the left costal margin. There were rhonchi and scattered rales through the lung fields and a marked tachycardia was present. Both tympanic membranes as well as the pharynx were moderately reddened. The remainder of the examination revealed essentially no abnormalities.

The patient's course was a stormy one, characterized principally by high spiking fever ranging between 101°F. and 107°F., by rapid respiratory rate with intermittent cyanosis, frequent passage of large bulky black stools, recurrent nose bleeds and bleeding from the site of venipunctures and during the terminal stages by vomiting of dark blood. There was no apparent response to various forms of therapy which included blood transfusion, intravenous fluids, aureomycin® and penicillin, and one intravenous injection of 2-hydroxystilbamidine. The patient died on December 19th, three days after admission.

During her hospital stay the following laboratory data were noteworthy:

1. The blood count on December 17, 1952, revealed a hemoglobin of 5.3 gm., red count of 2.84 million, reticulocyte count 3.0 per cent, platelets 5,600 per cu. mm., white count 4,100 per cu. mm., with 78 per cent neutrophils, 2 per cent eosinophils and 20 per cent lymphocytes. There was marked hypo- and polychromasia and poikilocytosis. Occasional H. capsulatum were found in the peripheral blood. There were 40 normoblasts per 100 white cells. The sedimentation rate was zero; mean corpuscular volume 74, mean corpuscular hemoglobin 18, mean corpuscular hemoglobin concentration 25.

2. Urine showed a 1+ to 2+ albumin with occasional white cells on microscopic examination. Specific gravity ranged between 1.009 and 1.015.

3. H. capsulatum was cultured from both the blood and the bone marrow on December 17, 1952. The marrow was heavily parasitized with H. capsulatum. (Fig. 20.)

4. Roentgenogram of the chest revealed exaggerated markings in both lung fields with a slight pleural reaction on the right. Review of films in the light of necropsy findings failed to permit roentgen identification of the primary foci.

Autopsy. Externally there were no superficial lymph node enlargements or edema. Pertinent findings were limited to the internal examination.

The pleural surfaces were dotted with petechiae. Delicate fibrous adhesions were present between the right upper and right middle lobes. The right and left lungs weighed 180 and 140 gm., respectively. In the subpleural region of the right middle lobe were two separate nodules, each measuring 3 mm. in diameter. They were firm, discrete and associated with fibrinous pleural thickening. When sectioned

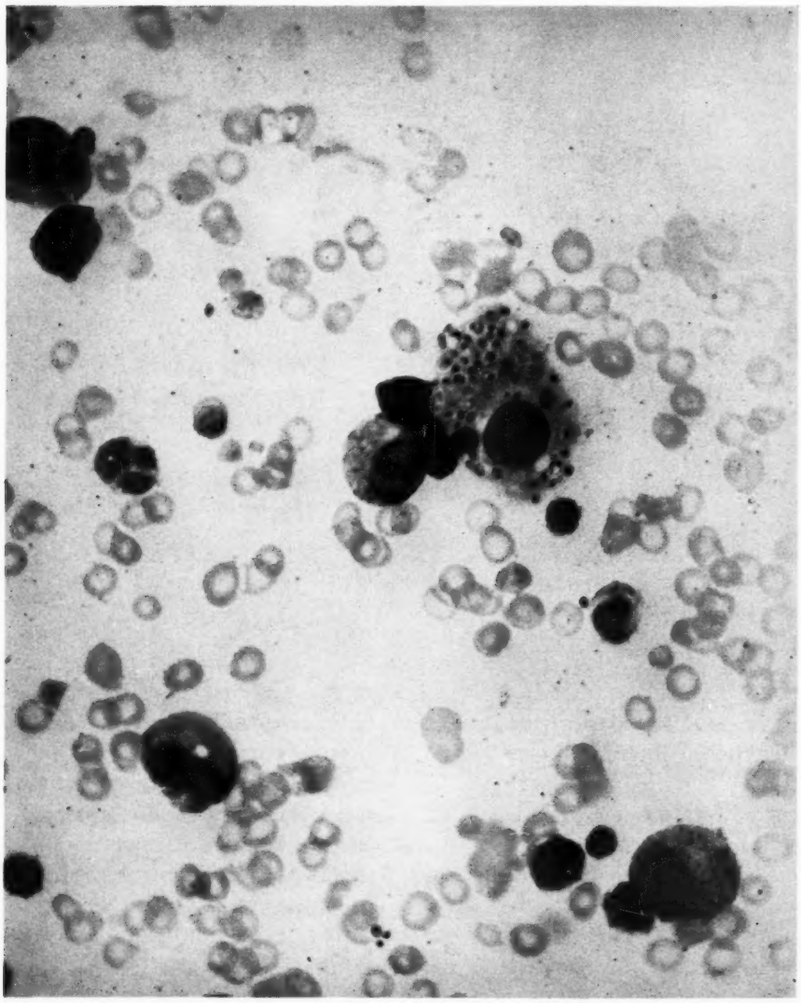


FIG. 20. Case 1. Bone marrow smear; numerous intracellular organisms and isolated group of three extracellular yeasts in lower part of field; original magnification × 650.

they were yellow, soft and contained enough calcific material to be gritty. There was a matted mass of lymph nodes at the right hilus measuring 2.5 by 1.5 cm. Individually they were nodular, firm, white and with stellate areas of yellow necrosis, resembling caseation. Calcification was not apparent. The other tracheobronchial lymph nodes were slightly enlarged but free from focal change. The lung substance was diffusely non-crepitant and consolidated. Sections revealed reddish-tan, firm, granular tissue which was somewhat friable. The process was most prominent in the posterior and apical segments of the right upper lobe.

The liver weighed 950 gm. and extended 6 cm. below the costal margin. The cut surface was yellow-tan, pale and mottled. An occasional grey nodule, 1 mm. in diameter, was noted.

The spleen weighed 150 gm. Scattered grey tubercles, to 1 mm. in extent, were visible on the capsular surface. Sections revealed occasional small irregular areas suggestive of confluent granulomas. Two accessory spleens, 1 cm. in diameter, showed similar change.

Throughout the small intestine and colon, most prominent in Peyer's patches, were follicular areas of erosion and hemorrhage. They were firm, considerably elevated and up to 2 mm. in diameter. The appendix revealed no abnormality. In the transverse colon were four polypoid lesions 1 cm. in greatest extent. They were firm, ovoid and button-like. Central erosions were coated with hemorrhage and a membranous exudate. The colonic wall in this area was thickened, indurated and adherent to a matted mass of mesenteric lymph nodes measur-

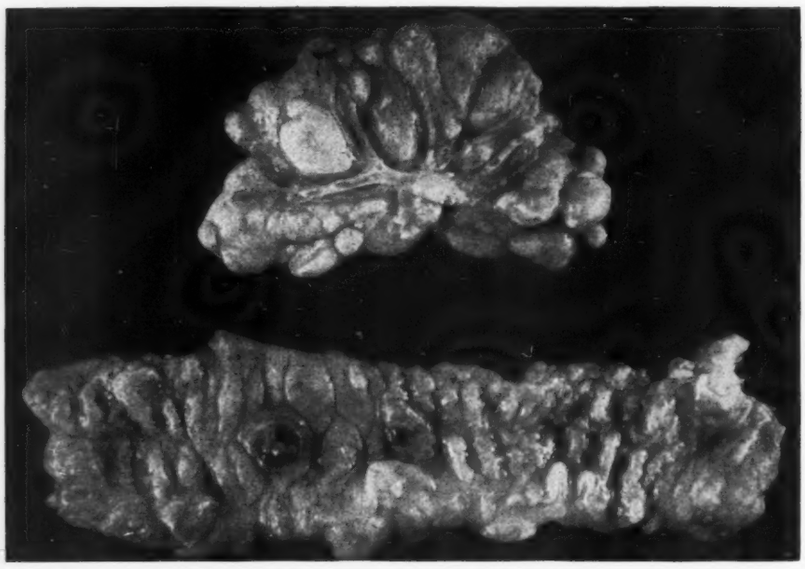


FIG. 21. Case I. Ulcerative colitis and mesenteric lymphadenopathy in presence of typical pulmonary primary complex.

ing 15 by 12 by 3 cm. These and confluent groups of periaortic and peripancreatic nodes resembled the tracheobronchial nodes when sectioned. (Fig. 21.)

The bone marrow and the adrenals revealed no abnormalities upon gross examination.

Microscopic Examination. The two subpleural nodules were of similar appearance. Central areas of necrosis and early calcification were rimmed by dense collagen and very little inflammatory reaction except for a few lymphocytes and giant cells. (Fig. 22.) Throughout the lung there was thickening of alveolar septa and interstitial fibrosis. Infiltration of histiocytes and lymphocytes, and occasional thrombosed capillaries were seen in the framework. Extruded into alveolar spaces and often packing them were large numbers of histiocytes and multinucleated giant cells. Within the nodules and also within the alveolar histiocytes were innumerable organisms (H. capsulatum). In tracheobronchial, mesenteric, pericolic and retroperitoneal lymph nodes there were nodular areas of caseation necrosis intermixed with collagenous scarring, but little tubercle formation or giant cell reaction was noted. Thousands of fungi were seen.

In the spleen there was a diffuse infiltration of the cords and sinusoids by great numbers of histiocytes, all of which were packed with H. capsulatum. Necrosis or frank tubercle formation was not seen.

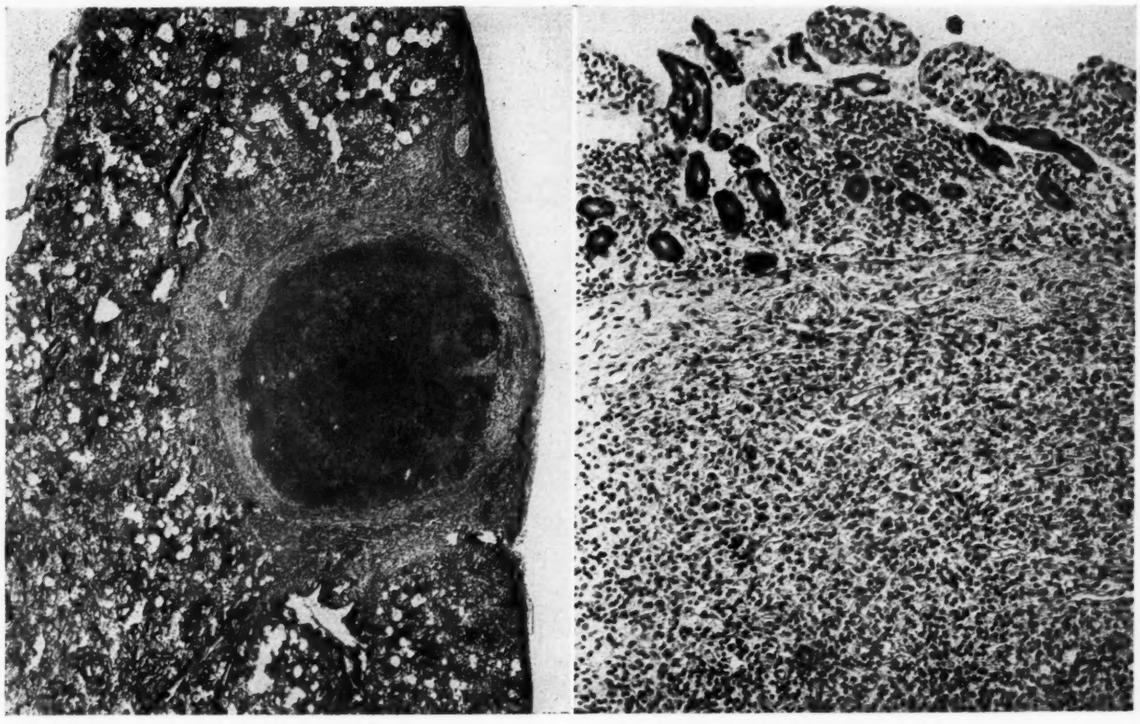
Throughout the lobules of the liver, irregular collections of histiocytes were present, sometimes in small nodules. Minute foci of necrosis with early fibrosis and a few multinucleated giant cells were occasionally encountered. Again, a multitude of fungi was seen.

The involvement by H. capsulatum of the intestine and colon had a distinct predilection for the lymphoid tissue. The scattered mucosal follicles and Peyer's patches were the site of nodular aggregations of histiocytes which were packed with fungi. (Fig. 23.) On the mucosal aspect there was necrosis, ulceration and microabscess formation. The larger polypoid lesions in the transverse colon were an exaggeration of this change. Also encountered in the larger lesions were foci of acute necrosis and bacterial invasion extending into the pericolic fat.

One adrenal revealed a single minute nodular infiltrate of histiocytes, containing fungi.

The bone marrow revealed a diminished content of hemopoietic elements although there was a recognizable erythroid hyperplasia. The striking feature was a diffuse and intense infiltration by histiocytes which were packed with H. capsulatum. Necrosis or tubercle formation was not seen.

CASE II. M. S., a white female, four years and one month of age, was admitted to Children's Hospital on December 17, 1952, when it was learned that she was not well and had swollen glands in her neck. (Fig. 24.) Her



22 23

FIG. 22. Case 1. Primary focus of the lung; well circumscribed necrotic focus with fibrous wall and slight pleural involvement; original magnification × 17.

FIG. 23. Case 1. Mostly diffuse mononuclear cell infiltrate of mucosa and deeper layers of small bowel; note absence of true ulceration, indicating that the infiltrate is not due to infection from the intestinal lumen. Original magnification × 150.

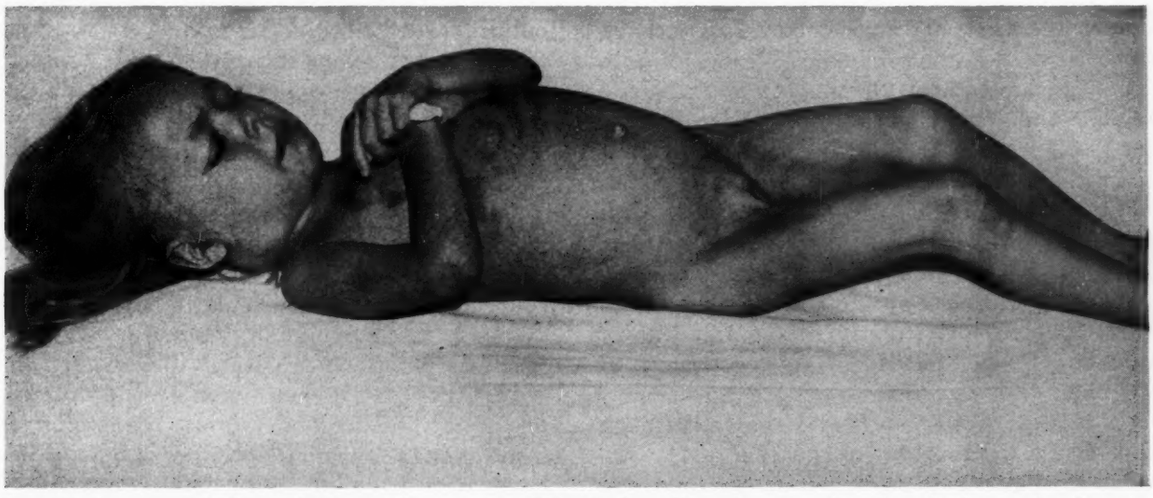


FIG. 24. Large cervical lymphadenopathy; stupor; abdominal swelling due to ascites, lymphadenopathy, hepatosplenomegaly and meteorism. Note atrophic lower extremities.

sister, C. S., admitted the day before, had been found to have acute disseminated histoplasmosis, proved by examination of the bone marrow.

Both children became ill approximately three weeks before admission to the hospital. M. S. developed progressive painless enlargement of cervical lymph nodes and slight cough; there was no change of appetite, which had been generally poor, no recognized fever, weight loss, abdominal enlargement or other evidence of systemic disease.

Physical examination on admission revealed a

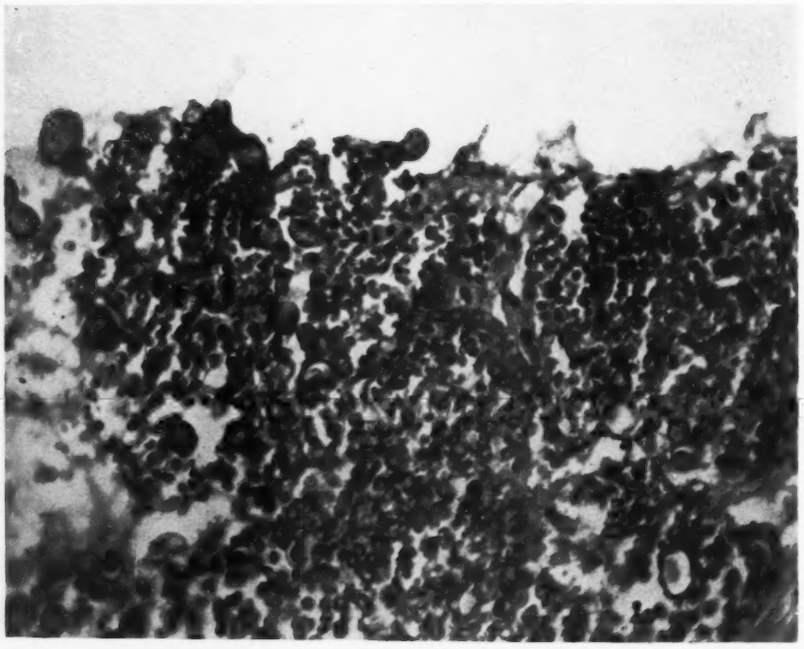


FIG. 25. Lymph node (Case II); small and large cells of Histoplasma capsulatum close to surface of tissue explant after ten days; original magnification × 650; periodic acid Schiff stain.

thin, poorly developed and poorly nourished girl who appeared chronically ill. Massive enlargement of lymph nodes on both sides of the neck resembled the classical picture of Hodgkin's disease in adults. The masses of nodes were matted together, were firm and non-tender and were not adherent to the overlying skin, which was not reddened. Nodes of 1 to 3 cm. were present in the axillary and inguinal regions and were firm and non-tender. Except for a soft systolic murmur heard by one examiner, the examination of the heart and lungs was not remarkable. The abdomen was distended, the liver and spleen were both easily palpable. Irregular masses, thought to be enlarged intra-abdominal lymph nodes, could be palpated in the abdomen, particularly in the right lower quadrant. The patient was conscious but irritable.

Laboratory examinations were undertaken specifically with respect to isolation of H. capsulatum. Blood cultures taken on the following dates were all negative: December 18, 23, 24, 28, 1952 and January 5, March 24, 1953. Bone marrow aspiration of the spinous process and sternum performed on December 18, 1952, and January 9 and March 25, 1953, revealed all smears to be negative; cultures were positive after each aspiration except on January 9th. Examination of the stools on April 7 and 8 and May 12, 13, 14, 1953 revealed them all to be negative for H. capsulatum. Cervical nodes (Fig. 25) showed the following: A biopsy performed on December 29, 1952 revealed smear, culture and section to be positive; aspiration performed on February 4, 1953 revealed the culture to be positive; incision and drainage were performed on February 8, 1953; drainage swab on March 16, 1953 revealed the culture to be positive, drainage swabs on April 8 and April 27, 1953 gave negative results from the cultures.

Other laboratory procedures and their results were: blood count on admission: 8.2 gm. hemoglobin; 3.94 million red blood cells; 2.24 per cent reticulocytes; 230,000 platelets; 9,100 leukocytes; 71 per cent polymorphonuclears; 1 eosinophil; 23 lymphocytes; and 5 mononuclears. Until April, 1953, there were several cycles of decreasing hemoglobin levels responding to transfusion; subsequent decreases of hemoglobin levels were irregular and relatively precipitate following episodes of massive gastrointestinal hemorrhage.

The white blood count ranged between 13,000 and 11,000 for the first three weeks. A marked leukopenia occurred on January 8, 1953, but by January 27th the white blood count had attained a level of 13,800 per cu. mm. Thereafter the white blood count ranged be-

tween 7,500 and 16,000. On March 17, 1953, there was a sharp rise to 30,700, after which time, except for occasional rises in the thirty thousand range, the count tended to run between 14,000 and 20,000. The differential counts during this period were not remarkable; the fluctuations were reflected chiefly in the percentage of polymorphonuclear cells which reached 91 per cent when the total count was in the thirty thousands. Smears of the blood at all times showed aniso- and poikilocytosis, hypochromia in the red blood cells and toxic granules and frequent immature forms in the white blood cells. No H. capsulatum were observed in any of the peripheral blood smears.

Urine examinations indicated normal concentrating and diluting power. Albumin, bacteria, white blood cells and occasional casts were generally present. Cultures were positive for Escherichia coli, paracolon organisms and nonhemolytic streptococci on many occasions. Proteus morgagni was isolated from the stools, which contained both gross and microscopic blood. Examination of the cerebrospinal fluid on four occasions revealed no abnormalities. Chemical studies of the blood were not remarkable except with respect to the protein fractions. The results are indicated below:

Date	Total Protein (gm./100 cc.)	Albumin (gm./100 cc.)	Globulin (gm./100 cc.)
12/22/52	7.9	3.6	4.3
1/5/53	6.6	...	...
1/20/53	7.4	3.0	4.4
2/10/53	7.0	2.5	4.5
3/16/53	6.8	2.9	3.9

The cephalin flocculation test was 3+ on December 22, 1952, but gave negative results from several determinations thereafter. On December 28th electrophoresis of the plasma revealed the following composition of the protein fractions: albumin 37 per cent, alpha-1 7 per cent, alpha-2 14 per cent, beta 14 per cent, and gamma more than 28 per cent.

Skin sensitivity to purified protein derivative and to histoplasmin (Lilly) in dilutions of 1:1000 and 1:100 was consistently negative. Complement fixation test for histoplasmosis gave positive results in a dilution of 1:512 on December 18, 1952, while the precipitin test gave positive results in a 1:2 dilution.

Clinical Course. Although proof of the diagnosis in M. S. was not obtained until later, isolation of H. capsulatum from the marrow of her sister made the clinical diagnosis of histoplasmosis almost certain. Therefore, this patient was started on a course of treatment with 2-hydroxystilbamidine* on December 19, 1952, the day after admission. Transfusions were administered practically simultaneously because of the severe anemia. For about three and one-half weeks the child had daily afternoon and evening temperature elevations generally spiking to 104°F. She was withdrawn and relatively quiet but otherwise the sensorium was normal. The cervical glands continued to enlarge. On December 29th four lymph nodes were removed from the left side of the neck; direct smears were positive for H. capsulatum and subsequent cultures and histologic sections gave positive results. About the end of the third week in the hospital she was given another transfusion of fresh, citrated blood from her uncle whose skin test for histoplasmin had given strong positive results. At the same time the dosage of 2-hydroxystilbamidine, which was administered intravenously originally and then intramuscularly, was increased to 120 mg. again by the intravenous route. The following day the child became suddenly worse, the temperature rose to 107°F. and mottled cyanosis and dyspnea appeared.

In the next three to four days, after the administration of procedures designed to reduce temperature and the use of an oxygen tent, a rather surprising improvement took place. The temperature continued to be intermittent but the maximal temperature reached was generally between 100° and 101°F. At the same time the clinical appearance of the child improved. This clinical improvement was maintained, except for progressive enlargement of the cervical lymph nodes, until the end of the sixth hospital week when a gradual increase in the amplitude of the temperature swings was noted. Early in the eighth week the lymph nodes in the neck became fluctuant and this was confirmed by aspiration. H. capsulatum were still present. 2-Hydroxystilbamidine, which was discontinued after the acute distress of the fourth week, was resumed in smaller dosage by intramuscular

* Material and guidance supplied by Dr. I. Snapper, N. Y.

injection. The cervical incisions were secondarily infected with H. staphylococcus aureus. Antibiotic therapy was instituted.

The patient continued to run the low grade septic temperature noted before incision and drainage of the cervical nodes. The mass in the right lower quadrant gradually enlarged; the child slowly became more irritable. She was not losing weight but no weight gain could be noted, and in fact she seemed to be slowly losing ground. She became progressively lethargic; at the end of the thirteenth week generalized twitching suddenly developed and the patient became unconscious. Convulsions occurred, some generalized, some unilateral, first on one side and then the other. There were short periods of lucidity but the sensorium clouded from that point on and tube or intravenous feedings were necessary. No localizing signs could be demonstrated and several examinations of the cerebrospinal fluid failed to demonstrate any pathologic change in its constitution.

Shortly thereafter, blood began to appear in the stools in large amounts. Earlier small amounts had been noted on occasion but these constituted massive hemorrhages and required transfusion. The draining incisions in the neck gradually healed.

The subsequent course was one of slow, relentless deterioration and death occurred August 25, 1953, eight months after admission to the hospital.

Autopsy. On external inspection the body was seen to be markedly cachectic and emaciated. Suppurative lesions were noted on the scalp and neck, with similar findings on the tongue. The pulmonary parenchyma showed little abnormality except for an occasional focus which will be described later. The regional lymph nodes were enlarged and showed varying degrees of fluctuation suggestive of caseation. Heart and spleen were without abnormalities. The abdominal cavity contained 200 cc. of serous turbid fluid and marked enlargement of the lymph nodes was noted. They varied in size from 5 to 25 mm. in diameter, were soft, and on sectioning showed marked formation of caseous foci. The liver was somewhat enlarged but without recognizable disease on cut surface.

There was a diffuse inflammatory process involving the entire small and large intestine. The small bowel, particularly in the ileum, had a diffuse pseudomembranous inflammation of yellow appearance. Focal areas of ulceration were seen, varying in size from 2 to 15 mm. in diameter. These ulcerations showed a tendency to encircle the intestine in a transverse manner. The ulcerations were undermined, had rolled edges and a yellowish necrotic base. The terminal ileum at the ileocecal valve and cecum showed hyperplastic granulomatous lesions of submucosa which often protruded into the lumen. These lesions showed no ulceration. The appendix was edematous, diffusely inflamed and showed marked suppuration.

The rest of the organs, including brain, showed little abnormality upon gross examination.

Microscopic Examination. In the lung a fibrocaseous focus of 3 to 4 mm. diameter was found, with beginning calcium deposits in the center; the focus was surrounded by a thin fibrous capsule. Within the capsule there was a small rim of giant cells and occasional epithelioid cells. Occasional histiocytes contained H. capsulatum which, however, were absent in the central necrotic parts. Some of the giant cells also contained organisms. In addition to this focus, there were small groups of histiocytes in the interstitial and in the interalveolar space of the different lobes of the lung containing small numbers of organisms. These groups did not form tuberculoid structures and no epithelioid cells were found.

In the small bowel necrotic surfaces were seen with occasional ulceration. Very little exudative inflammation was noted, but numerous histiocytes with large numbers of H. capsulatum were seen in all layers. In other parts, there was extensive pseudomembranous inflammation with many polymorphonuclear leukocytes on the surface; below this layer followed one of histiocytes and, finally, lymphocytes predominated. Some of the ulcers have undermined edges. In still other parts, large tubercles of histiocytes were found containing innumerable organisms. These nodules produced bulging of the overlying mucosa which in parts was ulcerated. Mesenteric lymph nodes showed extensive epithelioid tubercles with necrosis (incomplete) and numerous organisms. In the colon the submucosal histiocytes formed tubercles containing numerous organisms, often without ulceration of the surface mucosa.

The kidneys, ovary, brain, pituitary and heart did not contain lesions related to histoplasmosis. There were some foci of semi-necrotic histiocytes containing H. capsulatum in the pancreas. No

nodule formation was noted. The spleen was congested but no organisms or reaction to organisms was noted. The bone marrow was markedly hyperplastic without evidence of histoplasmosis. In the liver there were small granulomas composed of histiocytes with acidophilic cytoplasm but no recognizable organisms were found in the substance of the liver. There were focal degenerative changes in the brain without recognizable relation to histoplasmosis.

Comments on Cases I and II. These children represent the fulminating (Case I) and chronic progressive (Case II) forms of the disease as seen in childhood. Both children showed primary pulmonary complexes suggesting the respiratory portal of entry. Widespread dissemination of infection was the rule and massive gastrointestinal hemorrhages were serious complications in both children.

CASE III.* A. B., a seventeen year old, well developed, well nourished white female was admitted to the Jewish Hospital for the second time on October 31, 1952, with a chief complaint of generalized skin eruption.

The illness had begun in January 1952, when an isolated maculopapular eruption first appeared on the left arm. A month later a similar lesion appeared in the hip region. Subsequently maculopapular lesions appeared and disappeared all over the body except the face. Pruritus was severe, interfered with sleep and led to the first hospital admission on October 6, 1952. During this admission several antihistaminic drugs were given but provided no relief. Cortone® was administered beginning October 15th in the amount of 50 mg. at first and then 25 mg. every four hours thereafter. She was discharged as improved on October 22nd and the diagnoses made at that time were exfoliative dermatitis and neurodermatitis.

Following discharge from the hospital and withdrawal of cortone a marked recurrent reaction occurred. Skin lesions became markedly exfoliative and weeping, the patient was in constant distress, had fever of 101°F. and severe chills. Facial edema appeared and readmission to the hospital was necessary nine days after the patient had been discharged from the first admission.

Physical examination on October 31, 1952, revealed a maculopapular eruption, exaggerated in skin folds, covering the entire body. Some lesions were dry and red, others were crusted, and still others were weeping. Cervical nodes were moderately enlarged. Apart from the skin, no other body systems were abnormal.

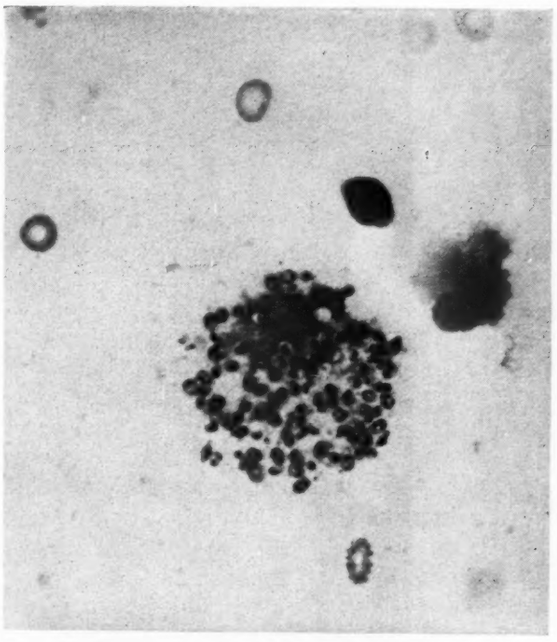


FIG. 26. Case III. Large cell from pleural exudate containing dozens of organisms; original magnification × 1000.

Laboratory examinations revealed the following: red blood cells 3.9 million; hemoglobin 11.5 gm.; white blood cells 10,300, 68 per cent polymorphonuclears, 9 per cent lymphocytes, 6 per cent monocytes and 17 per cent eosinophils. Serologic test for syphilis gave negative results. The urine contained 10 mg. of albumin and a few red cells. The chemical composition of the blood was within normal limits in all components studied.

The patient ran an intermittent fever ranging between 100°F. and 104°F. which was often associated with chills. No response to antibiotics was noted. On November 18, 1952, administration of ACTH was started; the temperature fell and the condition of the skin improved. At this time a heart murmur was noted in the apical and pulmonic areas, and diffuse abdominal tenderness was present. A small pleural effusion appeared. On November 21st H. capsulatum was identified in uncountable numbers in the pleural exudate (Fig. 26) and in the peripheral blood. (Figs. 27 and 28.) The patient was started on 2-hydroxystilbamidine. Her condition deteriorated and she died November 22nd.

* This case is presented through the kindness of Dr. H. Felson.

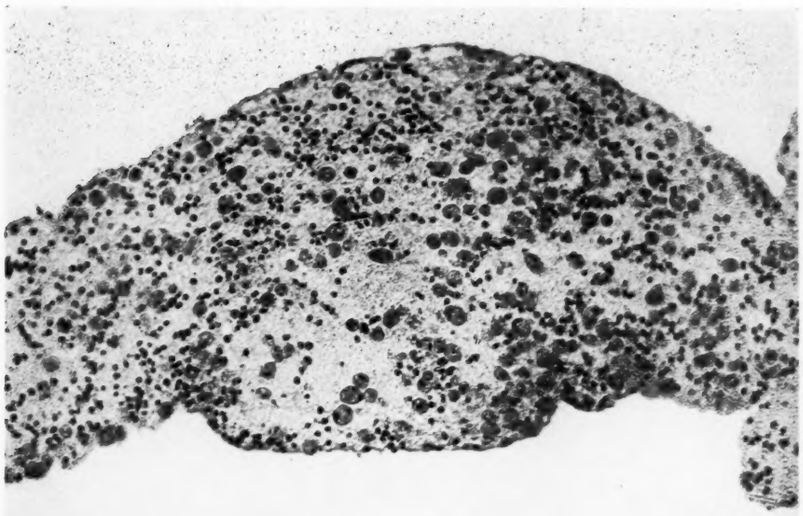


FIG. 27. Case III. H. capsulatum, 7000 colonies per cc. of blood, were counted. They were already visible after forty-eight hours; natural size of pour plate.

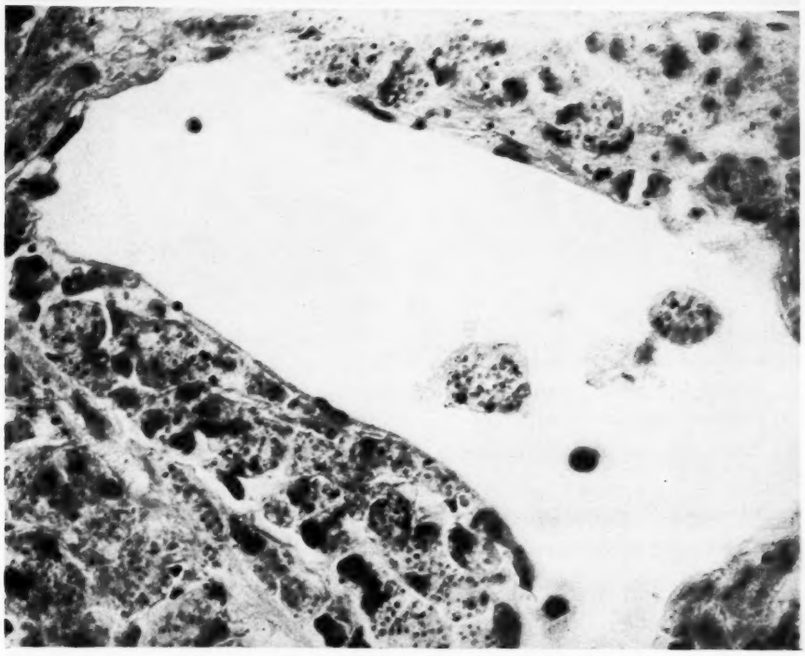
Autopsy. At autopsy, on external inspection, edema of the face, petechiae and scratch marks were prominent. (The serosal cavities all contained straw-colored fluid, the left pleura 800 cc., right pleura 500 cc., the pericardium 200 cc. and the peritoneum 300 cc.)

Organ weights: heart 280 gm., right lung 700 gm., left lung 600 gm., liver 2,700 gm., spleen 770 gm. and kidney 290 gm.

In the apex of the right lower lobe, there was a caseous focus of 10 by 7 mm. immediately below the pleura and the regional interlobular lymph nodes showed enlargement and caseation which was found also in a lymph node in the right inferior hilus. The rest of the thoracic lymph nodes were swollen but showed only spot-like foci of caseation. Tracheal nodules of 1 to 2 mm. were visualized and similar lesions were found in the left costal pleura. The lungs were solid throughout and only occasional miliary nodules on a diffusely brown background were recognized. Similarly, grayish nodules of 1 to 4 mm. were noted in the liver, the spleen, adrenals and kidneys. The gastrointestinal tract appeared normal on gross examination as was the heart, the internal genitalia, the thyroid and the pancreas. Microscopically, the primary lung focus contained a very large number of organisms and histiocytes which filled all alveoli or their remnants. There was complete loss of pulmonary architecture (but no caseation), and the overlying pleura showed fibrinous inflammation. The remainder of the lung showed innumerable histoplasma in phagocytes (Fig. 29), filling the alveoli, and less numerous interstitial (hematogenous) tubercle-like structures. Liver and spleen displayed unbelievable numbers of organisms with degenerative lesions of the parenchyma. Macrophages containing histoplasma were numerous in kidneys (Fig. 30), bone marrow (Fig. 31) and adrenals (Fig. 32), but were less numerous



28



29

FIG. 28. Case III. Blood clot taken from the heart with numerous parasitized phagocytes; original magnification × 160.

FIG. 29. Case III. Pulmonary vein; innumerable organisms in the phagocytes in the wall of the vessel and two cells in the lumen; original magnification × 650.

in skin, pancreas, thyroid and parathyroid. (Fig. 33.) The heart and the gastrointestinal tract were normal on microscopic examination. The lymph nodes throughout the body, in addition to the specifically described node formation related to the primary complex, were hyperplastic with enormous numbers of organisms in sinusoids and elsewhere.

Comment. This was a case of fulminating disease in a young adult in whom massive dissemination occurred while under treatment with adrenal cortical extract. The disease was so overwhelming and the organisms so numerous that they must have interfered with the function of organs in which they abounded by sheer mechanical displacement.

CASE IV.* E. B., a sixty-nine year old white man whose past history was not available, was admitted to Booth Hospital, Covington, Kentucky, June 4, 1951. In February, 1951, he had

* This case is presented through the kindness of Dr. D. Richfield.

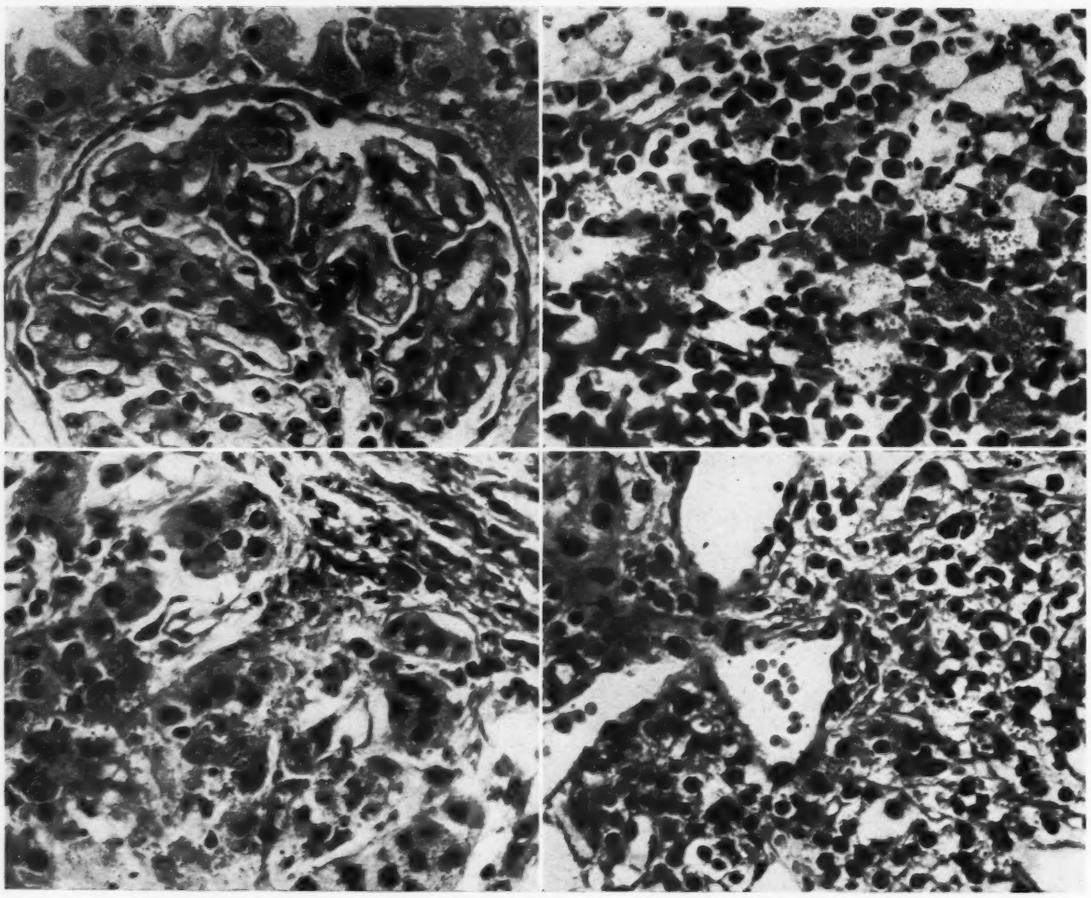


FIG. 30. Case III. In overwhelming invasion of the bloodstream all organs can become involved including the glomerular tufts; original magnification × 650.

FIG. 31. Case III. Bone marrow section; numerous organisms in swollen phagocytes; original magnification × 650.

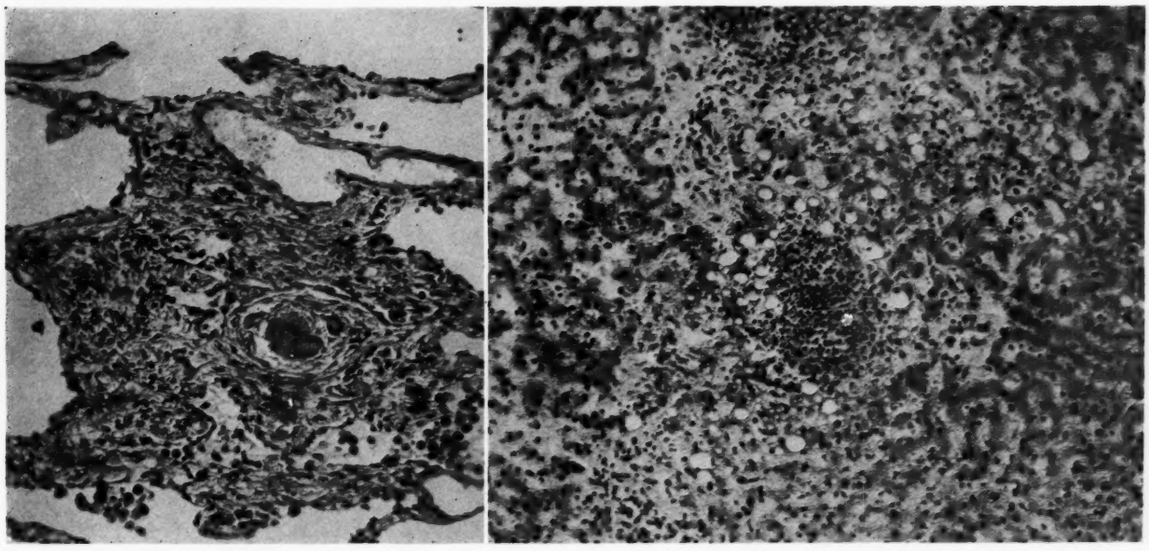
FIG. 32. Case III. Adrenal involvement; numerous intracellular organisms; original magnification × 650.

FIG. 33. Case III. Parathyroid involvement; original magnification × 650.

had an episode of cough and fever associated with positive roentgen signs of "pneumonia." He had been treated with penicillin; the response is not known. In April, 1951, roentgen examination of the gastrointestinal tract for unknown complaints was said to show "spastic colon and diverticula." Following this, without specific complaints, the patient became anorexic and gradually weakened. Shortly before admission to the hospital an acute decline occurred associated with cyanosis of the lips and mottling of the skin. In the belief that this represented "vasomotor collapse" administration of digitalis was begun on June 2, 1951, and he was also given lipoadrenal extract. Marked improvement occurred but was only temporary, and with return of somnolence he was hospitalized.

On physical examination he appeared chronically ill. He was dyspneic at bed rest; there was no cyanosis. The skin was sallow. The attending physician stated "it appears somewhat tan although he has not been in the sun." No lymphadenopathy was noted other than a left axillary node the size of a lima bean. The chest was mildly emphysematous. There was moderate non-tender hepatomegaly but no splenomegaly.

Laboratory data were as follows: The red blood count and hemoglobin within normal limits. The white blood cells numbered 5,000 to 7,000/cu. mm., but rose to 12,550/cu. mm. during the terminal stages. Initially, there was an eosinophilia of 21 per cent and a mild lymphocytosis; with cortisone treatment there was a gradual increase in neutrophils and stab cells, and a decrease in eosinophils and lympho-



34 35

FIG. 34. Case IV. Interstitial (hematogenous) fibrosing tubercle; original magnification × 160.

FIG. 35. Case IV. Submiliary necrosis and round cell infiltrates in liver; original magnification × 160.

cytes. Blood urea nitrogen was normal; bilirubin was 0.5 mg./100 cc.; total protein was 7.0 gm./100 cc. with the albumin comprising 2.8 gm. and the globulin 4.2 gm. A blood culture was sterile; urine was normal. Sputum was negative for acid-fast organisms. Roentgen examination of the chest demonstrated generalized miliary infiltration with left hilar enlargement with gradual but incomplete clearing. A needle biopsy of the liver was interpreted as showing miliary granulomatosis and fatty vacuolization; acid-fast stains gave negative results.

The patient was treated with antibiotics. Four days after admission a course of cortisone was begun; sudden improvement occurred on the eighth day of treatment and the patient went home when the drug was discontinued on the sixteenth day. There had been little febrile reaction at any time. Death occurred at home on July 12, 1951.

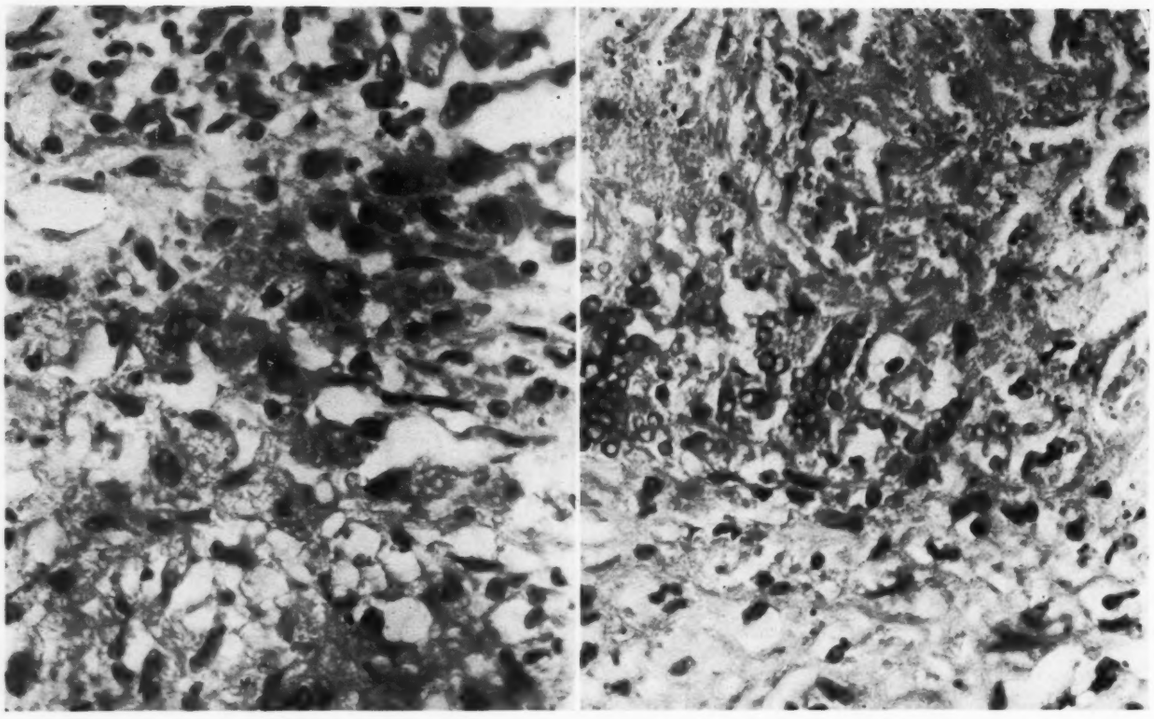
Autopsy. The body was that of a well nourished male of 165 cm. length and 75 kg. weight. The external inspection revealed no abnormality. In addition to extensive adhesions there were 100 cc. of straw colored fluid in each pleura. The right lung weighed 960 gm., the left lung 840 gm. A fine grayish granularity was more prominent in the upper lobes. The bronchial mediastinal lymph nodes were not remarkable. The liver was markedly enlarged (3,180 gm.) and showed miliary nodules. The spleen weighed 240 gm. The outstanding abnormality was found in the markedly enlarged adrenals (90 gm.) which were quite firm. Cortex and medulla were entirely replaced by reddish, grayish, yellowish mottled tissue. A small nodule was found in the pyramid of one kidney. Brain, heart and intestines were free of pertinent findings.

Microscopic Examination. In the lungs, a few interstitial tubercles were found which were very small and contained mostly epithelioid cells. (Fig. 34.) However, some foci had in addition numerous polymorphonuclear leukocytes. In some isolated spots H. capsulatum could be recognized definitely. All foci in the pulmonary parenchyma were of equal size.

Several lymph nodes of the bronchomediastinal region were examined and showed either scattered small abscess-like foci with polymorphonuclears and necrosis or the hyperplastic type of sinusitis with considerable swelling of the local histiocytes. Organisms in small number were recognized in some of the lymph nodes.

The spleen showed slight abnormality except for congestion but there were small circumscribed epithelioid tubercles between the otherwise normal cells.

In the liver were numerous foci, either small polymorphonuclear accumulations or necrosis plus polymorphonuclears. (Fig. 35.) No organisms were demonstrated in the liver lesion. Also



36A 36B

FIG. 36. Case IV. A and B, "small" and "giant" forms of H. capsulatum in the same adrenal; original magnification × 650; periodic acid Schiff stain.

present was an interstitial round cell myocarditis but no evidence of histoplasma was found. The outstanding observation was in the adrenals which showed complete caseation and some small typical organisms. In addition, there were a great number of yeast cells, of about 6 to 8 μ diameter, which stained quite differently from the usual histoplasma organism but in view of the demonstration of giant forms in tissue explants[180c] they can be accepted as representative for this species. (Fig. 36.)

In the bone marrow there were small foci of abscess-like metastases but no organisms were demonstrated.

Comment. This case represents a subacute or chronic form of histoplasmosis with hematogenous dissemination, manifested by foci in nearly all organs and diffuse caseation of the adrenals. Obviously, the patient could have overcome the hematogenous dissemination as shown by occasional scar formation in miliary nodules of the lung, if the destruction of the adrenal cortex had not produced an unsurmountable difficulty. This patient, like that discussed in Case III, was under treatment with cortisone.

CASE V.* B. S., a three year old white girl, had an episode of "acute pneumonia" in April, 1949, after three months' continuous residence on a farm in Kentucky. Prompt response to penicillin was noted although a blood count, taken twelve hours after institution of treatment, was said to be "inconsistent with pneumonia." Recovery from the acute episode apparently was complete in seventy-two hours.

However, subsequently the child was noted to be anorexic and irritable and became fatigued easily. Medical attention was sought approximately six months later. At this time, at the age of three and one-half years, the child was pale, had slight bilateral catarrhal otitis media and slight injection of the posterior pharynx. There were shotty submental and anterior cervical lymph nodes but no generalized lymphadenopathy was present. The percussion note was slightly impaired in the base of the chest on the right, and breath sounds were diminished in the same region. The liver edge was palpable 1 cm. below the right costal margin; the spleen was not felt. Hemoglobin was 72 per cent, white blood

* This case is presented through the kindness of Dr. Carl F. Wagner.

cells 14,400 per cu. mm. and the erythrocyte sedimentation rate was 17 mm. in one hour. Urinalysis gave normal results.

The patient was hospitalized for treatment and study. Tuberculin test gave negative results. A histoplasmin skin test gave positive results. Roentgen examination of the chest revealed enlargement of the right hilum and increased markings bilaterally consistent with pulmonary inflammatory reaction with hilar lymphadenomegaly. Although there was little febrile reaction, penicillin and chloromycetin were administered and the child was discharged after one week in the hospital.

During the hospital stay blood cultures were made for H. capsulatum and bone marrow was studied by smear and culture. Blood cultures were negative but positive cultures of H. capsulatum were obtained from two separate marrow aspirations. Only three of twenty-six plates which were inoculated gave positive results. Complement fixation studies gave positive results in a 1:20 dilution on several occasions and subsequently they gave negative results. The identification of the organism* was confirmed in two other laboratories.

Clinically, the child was well but pale and slow in developmental behavior for about six months after admission to the hospital. Only on supportive treatment of a dietary nature did she begin to improve, gain weight and become more active, and one year later was to all appearances a healthy child. The shadows in the roentgenograms gradually disappeared and questionable calcification was noted about eighteen months later.

Comment. This is an example of symptomatic non-fatal histoplasmosis which could easily have been missed had not careful mycologic studies been made. The symptoms were minimal and in no way indicated strong suspicion of histoplasmosis. They could easily have been overlooked, in which case later pulmonary calcification and positive skin sensitivity to histoplasmin would have had little definite significance. The finding of H. capsulatum in the bone marrow was almost incidental in this child, who had been discharged from the hospital as well fully two weeks before the diagnosis was established by the positive cultures.

CASE VI.† C. B., a twenty-three year old married university student, was admitted to the Jewish Hospital on April 20, 1953, because of increasing fatiguability, chills and fever, occasional arthralgia without swelling or redness of the joints and generalized malaise. The illness had begun three weeks prior to admission. The chills and fever had subsided with treatment by aureomycin but the other symptoms had persisted. A chest film prior to admission was reported to show "pulmonary congestion."

Past medical history was non-contributory. There had been no previous similar episodes. The patient had lived in the northeastern part of the United States all his life and had never been out of the country or visited the southern part of the United States or the West Coast.

Physical examination revealed a well developed and well nourished white man in no acute distress. Blood pressure was 130/75, pulse 96, temperature 99.6°F. Positive findings included a sharp, non-tender liver edge just palpable at the costal margin on deep inspiration. The spleen was also palpable but not tender. A few small, non-tender nodes were palpated in the anterior and posterior cervical chains and in the axillas.

The clinical impression on admission was fever of undetermined origin. Possible etiologic factors included virus pneumonia, infectious mononucleosis, histoplasmosis or tuberculosis, blood dyscrasia and brucellosis.

The patient's nine-day hospital course was characterized by an intermittent fever with diurnal elevation of 99.8°F. in the afternoon and a gradual decline to 97.8°F. by the next morning. Roentgen examination of the chest was reported to demonstrate enlargement of hilar shadows and some widening of the mediastinum. A battery of diagnostic procedures was undertaken. These included a complete blood count, sedimentation rate, heterophile agglutination, cephalin flocculation, thymol turbidity, alkaline phosphatase, total protein and A/G ratio, Van den Bergh test, prothrombin time, agglutinations for typhoid, paratyphoid, brucellosis, cold agglutinin titer, blastomycosis and histoplasmosis complement fixation test, stools for culture, ova and parasites, blood cultures, bone marrow aspiration, and tuberculin and histoplasmin skin tests. The histoplasmin skin test gave positive results, the sedimentation rate was 29 mm./hour and the prothrombin time was 60 per cent of normal; the remainder of the tests gave normal results except for one blood

* Initial isolation performed by Miss Dorothy Artis.

† This case is presented through the kindness of Dr. H. Felson.

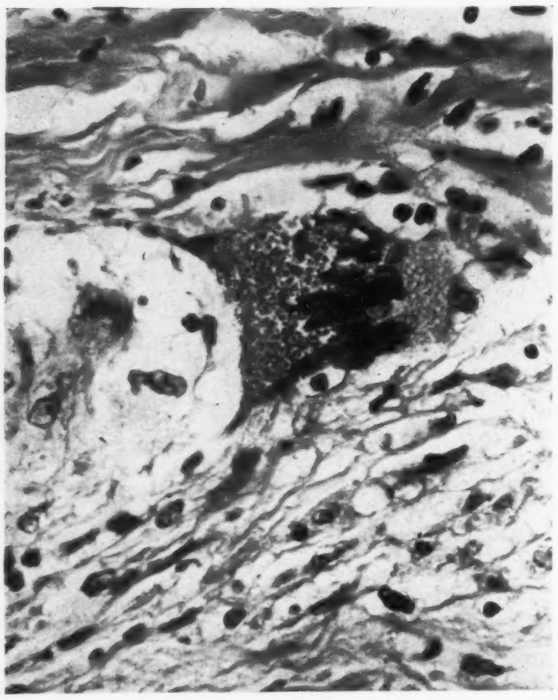


FIG. 37 Case VII. Epithelioid cells and multinucleated giant cells with numerous intracellular organisms; the greater part of the lymph node was calcified and partially ossified; original magnification × 800.

culture from which H. capsulatum was isolated the day after the patient left the hospital, improved but with his condition not diagnosed. At the time of discharge the intermittent fever persisted but the patient was subjectively better. Complement fixation was and still is (June, 1954) strongly positive, but fourteen months after the acute episode the patient is in excellent health.

Comment. This is another example of symptomatic non-fatal histoplasmosis in which the diagnosis would have been missed without mycologic cultures. Clinically, the patient had a mild to moderate fever of unknown origin from which recovery was taking place at a time when H. capsulatum were present in his blood stream.

CASE VII. B. J. S., an eleven year old white girl, was admitted to the hospital for surgical treatment of a patent ductus arteriosus. The clinical history and physical findings were typical for uncomplicated patency of the ductus arteriosus. The examining physician did elicit a history of recurrent "bronchitis" as a younger child. The anticipated treatment was carried out successfully and the patient is now clinically normal.

In preoperative roentgenograms of the chest, in addition to characteristic features of the cardiac malformation, a calcification was noted in intimate relationship to the dilated pulmonary artery. (Fig. 18.) Because of its accessibility to the area of surgery, the calcifying lymph node was removed by the surgeon at our request.

The lymph node measured approximately 12 by 8 by 6 mm. and was in its major part calcified. Microscopically (Fig. 37), numerous and fairly large foci of calcification were surrounded by areas with active granulomatous proliferation. There were small foci of histiocytic proliferation and a small number of multinucleated giant cells were seen. There was also caseation between the calcific masses. Occasional giant cells and histiocytes contained numerous organisms which were morphologically consistent with H. capsulatum. The culture from the lymph node and injection of the material into eight mice and reculture gave negative results, which probably reflects the fact that the organisms were not viable.

Comment. This patient illustrates the inapparent form of the disease for which positive proof in the past has been lacking or at best very scarce. It might be inferred, from evidence derived from the roentgenograms of intrathoracic calcification in this tuberculin-negative, histoplasmin-positive child, that the calcification and skin sensitivity were due to histoplasmosis, but in the absence of cultural or histologic proof this common combination of observations would have only statistical support.

SUMMARY

Histoplasmosis, once an "obscure" fungus disease, is recognized with increasing frequency, especially in the endemic area comprising Ohio, Kansas, Missouri, Indiana, Illinois, Kentucky and Iowa.

The disease is most frequently acquired by inhalation of spore-containing dust. The organism has been repeatedly recovered from soil and has given origin to local outbreaks in the form of small epidemics.

Hepatosplenomegaly and anemia with leukopenia occur in children. A picture very similar to any pulmonary disorder caused by tuberculosis is found in adults. Ulcerations in the oronasal region seem to be quite prevalent in adults.

The pathology of the disease is characterized by invasion of histiocytic elements by the

organisms. These multiply within the cells, which may become greatly enlarged. A productive and exudative response to the organism may be observed in many organs.

The skin test is an excellent epidemiologic tool and may also call attention to the possibility of histoplasmosis in clinical practice. However, only identification of the organism can be accepted as conclusive proof of disease, although a positive complement fixing test, especially with rising titer, contributes to a presumptive diagnosis.

The organism can be cultured successfully from many sites but bone marrow and blood are preferred. Sputum, bronchial washings and gastric lavage generally have to be injected into mice in order to avoid overgrowth by contaminating organisms. Liver and other biopsies may be decisive in establishing the diagnosis.

The mycologic diagnosis can be established by demonstration of the tuberculate spores produced at room temperature; the change of phase is an essential determinant in confirming the diagnosis. Sabouraud's glucose-agar or blood-agar are ideal media for isolation and identification of the organism.

Histoplasmosis has been found in several lower animals. In the laboratory, mice are ideal experimental subjects both for primary isolation and virulence studies.

No specific treatment is at present available; the value of surgical removal of lung lesions will have to undergo the scrutiny of time. If current estimates that 20 to 30 million people in the United States have histoplasma infections are correct, the magnitude of the problem becomes obvious. It is also apparent that histoplasmosis is a benign disease which only in exceptional cases becomes symptomatic and dangerous.

Seven hitherto unreported cases are described. In the endemic area many patients, upon initial examination, reveal active or healed lung lesions in the presence of positive histoplasmin and negative tuberculin reactions.

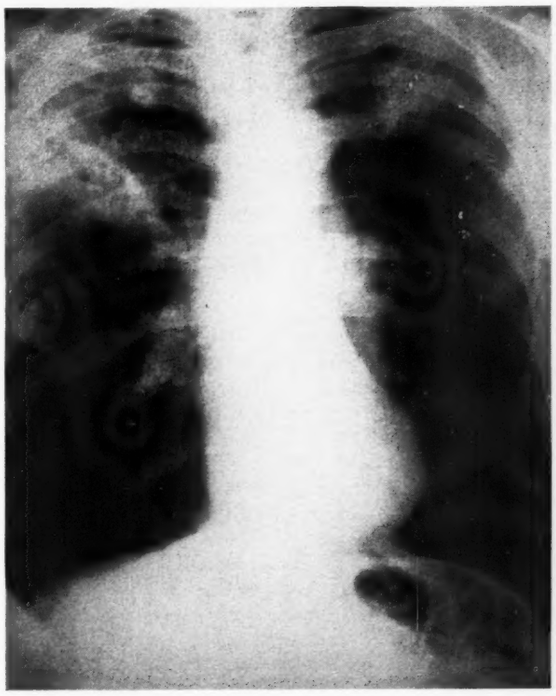


FIG. 38. Man, age 55; proved histoplasmosis, chronic progressive type; cough, hemoptysis and weight loss for one year; carcinoma of lung also present; H. capsulatum apparent from sputum and gastric lavage by culture.

ADDENDUM

Since the preparation of this paper several other proved cases of histoplasmosis have been encountered. Among them was a fifty-five year old negro who had had cough and hemoptysis for one year associated with marked loss of weight. Studies for tuberculosis gave consistently negative results; material removed on bronchoscopy, by biopsy and by suction demonstrated carcinoma, but cultures and animal inoculation of the same material revealed Histoplasma capsulatum. Roentgen examination of the chest disclosed widespread densities in the upper portions of both lungs and definite cavitation. (Fig. 38.) This case is typical of the chronic progressive form in adults and is an example of histoplasmosis complicating other chronic lung disease, in this instance, carcinoma. The discovery of this and several other cases not included, further emphasizes that careful mycologic studies are necessary in the endemic area to permit recognition of the role played by H. capsulatum in morbidity and mortality.

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Seminars on Carbohydrate Metabolism

Spontaneous Hypoglycemia*

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IT has gradually became apparent to most physicians that periodic spontaneous hypoglycemia is the cause of significant and sometimes alarming symptoms in a relatively large number of patients. A widespread diagnostic awareness of the "hypoglycemic syndrome" as a cause of periodic symptoms has been finally induced as the result of a number of reviews[1–7] on the subject published during the past twenty years. Whereas formerly many such patients went undiagnosed because hypoglycemia was not considered, the diagnosis is now being made promiscuously and without the supporting evidence necessary to establish it.

This presentation has four major purposes: (1) to outline again the whole problem, incorporating recent additions to our knowledge and rejecting discredited concepts; (2) to demonstrate the clinical usefulness of a few simple but rigid criteria in establishing the specific etiologic diagnosis in more commonly encountered and confusing types of spontaneous hypoglycemia; (3) to discuss rational therapy for the various types, based upon present concepts of the abnormal mechanism which produces hypoglycemia in each instance; and (4) to attempt to prevent unnecessary pancreatic explorations and subtotal pancreatectomies in patients who exhibit no indication for such procedures.

DEFINITION OF SPONTANEOUS HYPOGLYCEMIA

Spontaneous hypoglycemia is not a disease. It is an indication of a derangement in the over-all utilization of carbohydrate in which glucose has been removed from the blood at a rate faster than it has been replenished, with a resultant depression of the blood sugar to an abnormally low level. As will be indicated later, many organic and functional lesions exist, any one of which is capable of increasing the rate of removal of glucose from the blood and/or of decreasing its rate of entry into the blood. Recognition of this fact constitutes the first step toward an intelligent appraisal of the mechanism by which hypoglycemic episodes are produced in any given patient.

By definition the term excludes hypoglycemia induced by the administration of exogenous insulin, but in the evaluation of the patient suffering from spontaneous hypoglycemia the possibility of a factitious cause (self-administration of insulin) must always be in mind. Also, by definition, the term excludes the concept of "relative hypoglycemia" which has crept into the literature to cause confusion in both diagnosis and management. Patients with vague emotional or gastrointestinal symptoms whose blood sugar levels, either when symptomatic or in the course of a glucose tolerance test, remain essentially normal are said to have "relative hypoglycemia."[8–10] It is implied that such individuals are unusually sensitive to minor depressions of blood sugar values. In all patients with unequivocal spontaneous hypoglycemia, low blood glucose values (below 55 mg. per cent by the Folin-Wu method,[11] or below 40 mg. per cent by the Somogyi-Nelson method[12]) can be demonstrated repeatedly. The conditions under which such diagnostic levels occur will aid greatly in disclosing the nature of the abnormality.

It should be clear now that spontaneous hypoglycemia and hyperinsulinism are not synonymous terms. The former is the generic term. It includes all clinical situations in which the blood sugar may fall to abnormally low levels spontaneously. The term hyperinsulinism

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is confined to those types of spontaneous hypoglycemia in which an absolute increase in the production of endogenous insulin is believed to occur.

SYMPTOMS OF HYPOGLYCEMIA

Unusual manifestations of hypoglycemia as well as their relation to the actual level of the blood sugar have often caused confusion in diagnosis. At opposite poles of the spectrum of symptoms are two distinct clinical pictures. The appearance of one pattern or the other, or of a combination of the two, is determined not only by the level of the blood sugar but also by the rate at which it has fallen and the duration of the hypoglycemia. If the rate of fall in blood sugar is rapid, the predominant early symptoms are those produced by compensatory hyperepinephrinemia. This mechanism represents an attempt to restore normal blood glucose levels by accelerating hepatic glycogenolysis.[13] The symptoms are those which are observed during a mild reaction after administration of too much soluble insulin, and consist of sweating, weakness, hunger, tachycardia and "inward trembling." Conversely, if the blood sugar falls slowly to low levels over a period of many hours, the manifestations are cerebral in type:[14] headache, visual disturbances, mental confusion, coma and convulsions. If the decrease in blood glucose is rapid, profound and persistent, the initial symptoms due to excessive circulating epinephrine merge with those of cerebral hypoglycemia.

When the blood sugar concentration remains low for most of the twenty-four-hour period, a situation which may occur in organic hyperinsulinism, the manifestations of hypoglycemia may be so bizarre as to be completely misleading.[6] Any aspect of the entire range of neurologic or psychiatric disorders may be mimicked, including sensory or motor loss of an extremity, hemiplegia, outbursts of temper, extreme depression or apparent catatonic schizophrenia. Despite the atypical nature of symptomatology in some individuals, it is of interest that the same complex of symptoms tends to recur in the same patient. In our experience periodicity of symptomatology represents a more important diagnostic hint of underlying hypoglycemia than the specific type of complaint which is offered. The repetitive nature of the complaint, occurring at fairly specific times during the twenty-four-hour period, should arouse suspicion. The demonstration of hypoglycemia during an attack, together with dramatic relief of symptoms with intravenously administered glucose, establishes only the non-specific diagnosis of spontaneous hypoglycemia. The specific etiologic diagnosis must now be established if rational and effective therapy is to be applied.

CLASSIFICATION OF SPONTANEOUS HYPOGLYCEMIA

It is beyond the intent of this presentation to attempt to discuss the body's complex physiologic mechanisms which, when properly integrated, result in normoglycemia. Mention of the more important tissues, organs and endocrine glands involved is sufficient to impress one with the multiplicity of possible aberrations which can upset the delicately balanced level of blood sugar. The list includes the central nervous system, the autonomic nervous system, the gastrointestinal tract, kidneys, liver, muscles, pancreas, adenohypophysis, adrenal cortex and medulla, and the thyroid.

Table 1 presents a classification of spontaneous hypoglycemia based upon etiologic factors. Some of the situations listed are associated only rarely with hypoglycemia, but are included for purposes of more complete classification. The more commonly encountered types will be discussed in detail.

TABLE 1

ETIOLOGIC CLASSIFICATION OF SPONTANEOUS HYPOGLYCEMIA
(Enlarged from original.[15])

1. Organic—recognizable anatomic lesion
   - A. Hyperinsulinism
     1. Pancreatic islet cell adenoma[7]
        - a. Single
        - b. Multiple
        - c. Aberrant
        - d. Associated with adenomas of other endocrine glands (parathyroid,[16] anterior pituitary[6,17])
        - e. Pancreatic islet cell "suspiciously malignant" adenoma (localized)
     2. Pancreatic islet cell carcinoma (with metastases)[5–7]
     3. Generalized hypertrophy and hyperplasia of the islets of Langerhans[18–20]
   - B. Hepatic disease
     1. Ascending infectious cholangiolitis[21]
     2. Toxic hepatitis[22–24]
     3. Diffuse carcinomatosis[25–28]
     4. Fatty degeneration[29] or "fatty metamorphosis"[30]
     5. Laennec's cirrhosis[31,32]
     6. Viral hepatitis[32,33]
     7. Chronic passive congestion in congestive heart failure[34]
     8. Glycogenosis (von Gierke's disease)[35,36]
   - C. Anterior pituitary hypofunction
     1. Destructive lesions (chromophobe tumors, craniopharyngiomas)[37–40]

TABLE 1 (*Continued*)

2. Atrophy and degeneration (Simmonds' disease)[41–44]
3. Surgical hypophysectomy[45]
4. "Pituitary myxedema"
   a. Thyroid hypofunction secondary to pituitary failure[46–48]
   b. Pituitary failure secondary to myxedema[49–52]
5. Severe inanition[53,54]
6. Postoperative hypoglycemia[55,56]

D. Adrenocortical hypofunction
1. Idiopathic cortical atrophy[57]
2. Destructive infectious granuloma[58]
3. Destructive neoplasm[59]
4. Congenital adrenal hyperplasia[60]

E. Fibromas and sarcomas[61]

F. Central nervous system lesions (hypothalamus or brain stem; interference with nervous control of blood sugar)[62–67]

II. Functional—no recognized anatomic lesion, but explainable on basis of unusual somatic function

A. Hyperinsulinism (imbalance of the autonomic nervous system); "hypoglycemic fatigue; nervous hypoglycemia; functional hypoglycemia, reactive hypoglycemia"[8,68–76]

B. Alimentary hyperinsulinism (rapid intestinal absorption)
1. After gastroenterostomy[77]
2. After partial or total gastric resection[77–82]

3. Hyperinsulinism of infancy (Staub-Traugott phenomenon)[51]

D. "Idiopathic spontaneous hypoglycemia of infancy"[51]

E. Renal glycosuria (severe degrees of low renal threshold for glucose)[83]

F. Lactation[84,85]

G. Severe continuous muscular work[86]

III. Factitious (surreptitious insulin administration)[87–90]

As an initial approach to placing a given hypoglycemic patient into his proper category etiologically, we have found it helpful to classify spontaneous hypoglycemia in still another way: the fasting hypoglycemias, the stimulative hypoglycemias, and those types in which both phenomena are demonstrable.

I. Fasting hypoglycemia: In this group the lowest level of blood sugar of the twenty-four-hour period is always obtained after the longest period without food. This usually means just before breakfast, providing a three-meal schedule is being followed during the day.

1. Hepatogenic hypoglycemia
2. Anterior pituitary insufficiency
3. Adrenal cortical insufficiency
4. Central nervous system lesions
5. Fibromas and sarcomas
6. Severe renal glycosuria

II. Stimulative hypoglycemia: This group exhibits consistently normal levels of the fasting blood sugar. It is two to four hours after the beginning of absorption of carbohydrate that hypoglycemia occurs. Measures designed to prevent the postprandial rise of blood sugar abolish the secondary hypoglycemic dip which follows it.

1. Functional hyperinsulinism
2. Alimentary functional hyperinsulinism
3. Hyperinsulinism of infancy

III. Combined fasting and stimulative hypoglycemia:

1. Organic hyperinsulinism
2. "Idiopathic spontaneous hypoglycemia of infancy"
3. Factitious (exogenous hyperinsulinism)

DETERMINATION OF ETIOLOGY IN THE INDIVIDUAL CASE

It will be clear from reviewing the etiologic classification that in most of the causes listed spontaneous hypoglycemia represents but one facet of an obvious clinical entity which is usually easily recognized. Thus one scans the patient first for clinical signs of adrenal or pituitary insufficiency, for central nervous system damage, for an abdominal scar which might indicate a gastric operation, for lactation or renal glycosuria, etc. Much less obvious is the rare case of self-administration of insulin. This possibility should come to mind when the patient is a nurse, physician, diabetic or a close relative of a diabetic who takes insulin. The suspicion is heightened when severe hypoglycemia occurs at unexpected times and without similarity of time pattern from day to day. The etiologic factors mentioned in this paragraph, however, represent the cause of symptomatic hypoglycemia is less than 15 per cent of the total number of cases encountered.

From the point of view of apparent difficulty in differential diagnosis, three causes of spontaneous hypoglycemia stand out and together they account for about 80 per cent of all cases. They are (1) functional hyperinsulinism, (2) organic hyperinsulinism and (3) hepatogenic hypoglycemia. Functional hyperinsulinism is the most common cause of symptomatic hypoglycemia and appears to be a psychosomatic disorder. The hypoglycemia, however, can be

controlled by rigid adherence to a high protein, low carbohydrate diet. Organic hyperinsulinism requires surgery. In this condition hypoglycemia is intensified by a diet low in carbohydrate and is only temporarily alleviated by one high in carbohydrate. Proper differential diagnosis of these two conditions results in selection of the proper patient for exploration of the pancreas, and avoids unnecessary subtotal pancreatectomies in those who had no indication for surgery in the first place.

Hepatogenic hypoglycemia may be acute and transient or chronic and persistent, depending upon the etiology of the diffuse hepatic lesion. The prognosis is dependent upon the etiology of the hepatic lesion. In most cases dietary control of the hypoglycemia (high protein, high carbohydrate diet with an extra feeding at bedtime) is all that can be offered. Occasionally, removal of the source of a chronic, active, ascending cholangiolitis (cholecystectomy) results in remarkable improvement in hepatic function with relief of fasting hypoglycemia.[21]

In attempting to differentiate these three important causes of spontaneous hypoglycemia, we have found the following guides to be of greatest value: (1) the history and clinical course of the disturbance; (2) the level of the fasting blood sugar: (*a*) on an average intake of carbohydrate, (*b*) upon restriction of carbohydrate or after a period of fasting; (3) the results of a glucose tolerance test performed after standard dietary preparation;[91] (4) the results of a battery of liver function tests.

Table II summarizes the usual distinguishing characteristics among the three types, and

TABLE II

Type of Hypoglycemia	Fasting Blood Sugar		Glucose Tolerance Curve	Liver Function	Clinical Course
	Standard Diet	CHO Restriction or 24 Hour Fast	After Standard Dietary Preparation		Progression and Time of Attacks
Functional hyperinsulinism	Normal	Normal*	Normal fasting blood sugar; sharp fall to hypoglycemic levels between 2nd and 4th hours	Normal	Not progressive in severity; more frequent under emotional or physical tension; relief by vacations, etc.; no prebreakfast attacks; attacks 2 to 4 hours after meals; no effect of skipped or late breakfast
Organic hyperinsulinism	Subnormal: usually below 50 mg. %	Subnormal: always below 40 mg. %; usually below 30 mg. %	Subnormal fasting blood sugar; low level curve;† sharp fall to very low levels between 2nd and 5th hours	Normal	Progressive in frequency and severity; prebreakfast attacks frequent from 2 A.M. to 8 A.M.; attacks 2 to 4 hours after meals; attacks precipitated by skipped or late meals, or exercise
Hepatogenic hypoglycemia	Subnormal: often below 50 mg. %	Subnormal: always below 40 mg. %; often below 30 mg. %	Subnormal fasting blood sugar; hyperglycemic plateau curve with glycosuria; gradual fall to hypoglycemic levels in 4 to 7 hours	Usually markedly diminished	Progressive in frequency and severity; prebreakfast the time of most frequent occurrence, 2 A.M. to 8 A.M.; daytime attacks rare unless precipitated by skipped meal; sometimes clinical evidence of hepatic disease

* During 3 days of severe carbohydrate restriction most normal people show fasting blood sugar levels of 50 to 60 mg. % (Somogyi).

† See text.

Figure 1 illustrates the characteristic oral glucose tolerance curve obtained in each.

CHARACTERIZATION AND MANAGEMENT OF SOME OF THE TYPICAL CLINICAL SYNDROMES WITH ILLUSTRATIVE CASES

Functional Hyperinsulinism

This is the only really common form of spontaneous hypoglycemia, and accounts for

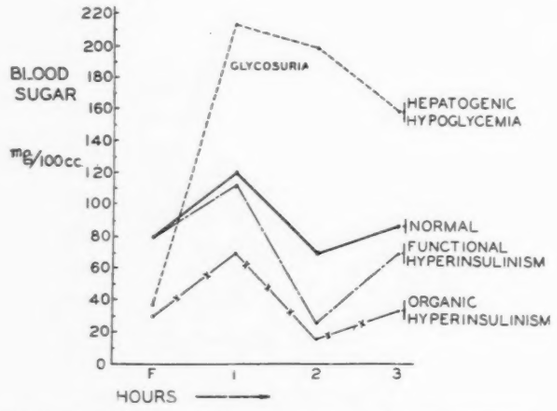


FIG. 1. Glucose tolerance curves in spontaneous hypoglycemia (three types).

about 70 per cent of all cases. Synonyms employed by various authors for this type of spontaneous hypoglycemia include: "hypoglycemic fatigue," "nervous hypoglycemia," "functional hypoglycemia" and "reactive hypoglycemia." The term functional hyperinsulinism seems preferable to us because it defines the most probable mechanism by which the hypoglycemia is produced.[15] All who have studied the problem agree that the disorder involves a disturbance in the finer regulation of the blood sugar by the vegetative nervous system.

Insulin-producing pancreatic islet cells secrete in response to a rising concentration of arterial blood sugar.[92–94] The influence of the autonomic nervous system upon this mechanism has received little study although vagal effects are probably important.[94,95] Until more information is available on this point, we choose to regard an increased vagal effect as increasing the sensitivity and responsiveness of the insulin-producing cells to a given rise of arterial blood sugar. Functional hyperinsulinism is thus considered to represent a hypersensitivity and an excessive responsiveness of histologically normal islet cells to the normal stimulus for insulin secretion. Under these circumstances a normal postprandial rise in blood sugar elicits an excessive secretion of insulin. The existence of concurrent emotional tension in such patients is beyond dispute. Demonstration that the postprandial secondary hypoglycemia exhibited by these patients is actually associated with hyperinsulinemia must await an accurate method for assaying circulating insulin.

The general physiologic and psychologic status of individuals subject to attacks of functional hyperinsulinism is interesting. They are intense, driving and intensely conscientious. They typify the so-called "vagotonic personality."[68,71] They are total hyper-responders, gastric hyperacidity and vasomotor instability being frequent concurrent manifestations of a general instability of the vegetative nervous system. Some authors have emphasized the obvious psychosomatic aspects of functional hyperinsulinism.[69,71,90] In many of these patients it is abundantly clear that after having established functional hyperinsulinism as a major cause of symptomatology, one is forced to make the additional diagnosis of an anxiety state. However, it is of practical importance to the patient that the hypoglycemia, which often produces his most troublesome symptoms, can be controlled by dietary means when environmental tensions persist.

Clinical Characteristics. 1. Relation of attacks to meals: The hypoglycemia is purely stimulative (postprandial) in type. It never occurs in the fasting state. Prebreakfast attacks do not occur, nor do symptoms develop during the morning when the patient omits breakfast. Symptoms occur only after meals and usually appear in two to four hours. The periodicity of symptoms in relation to time comprises the most helpful clue to the underlying disturbance.

2. Character of the symptoms: The manifestations of functional hyperinsulinism are essentially those of hyperadrenalinemia: weakness, hunger, "inward trembling," sweating and tachycardia. They are usually mild and transitory, often subsiding within fifteen or twenty minutes. Although early symptoms of cerebral hypoglycemia may supervene (diplopia, confusion, faintness, "black out spells"), it is a differential diagnostic point of great value that actual loss of consciousness or convulsions never occur in functional hyperinsulinism.

3. Progression of symptoms: In contrast to the intensification of symptoms with time observed in organic hyperinsulinism and hepatogenic

hypoglycemia, the manifestations of functional hyperinsulinism are not progressive. They tend to vary in proportion to the magnitude and persistence of environmental pressures.

4. The glucose tolerance test: The oral glucose tolerance curve is pathognomonic (Fig. 1) providing that standard dietary preparation is employed.[91] The fasting blood sugar is always normal, as is the absorptive rise. The secondary hypoglycemic phase, however, is rapid and profound. Unless levels below 40 mg. per cent (true blood sugar) can be demonstrated, the test is not regarded as diagnostic. It is imperative that blood samples be obtained at half-hour intervals after the second hour of the test for two additional hours. Almost invariably the patient's characteristic symptoms occur during the test, and the time of symptoms coincides with the time that hypoglycemia occurred.

Illustrative Case. Patient N. P., a twenty-eight year old single, female, art teacher, was admitted on April 16, 1954, complaining of recurrent spells of sleepiness and epigastric pain of three years' duration. These occurred usually late in the morning or afternoon, but occasionally about 9 P.M. They were accompanied by sweating, "inward tremor," weakness and a sense of loss of contact with her surroundings. Palpitation was noted during some episodes, and blurred vision during others. Attacks usually lasted fifteen to twenty minutes and, although she had "almost blacked out" several times, actual loss of consciousness had never occurred. The patient recognized a definite correlation between the frequency of attacks and physical or emotional exhaustion resulting from excessive hours of work. Benzedrine had afforded no relief of symptoms. For a three-month period, however, she had noted relative freedom from spells while following a self-devised high protein diet divided into six feedings daily. Symptoms recurred promptly after returning to a normal three-meal diet. Except for these episodes she considered herself to be entirely well.

On physical examination the patient's general health appeared to be excellent. Her personality pattern was an admixture of intense, driving energy and effusive, pleasant and outwardly calm demeanor. She blushed frequently and large areas of vasodilatation on neck and chest remained after facial flushing disappeared. Dermatographia was demonstrable. The palms were cool and clammy. The remainder of the examination revealed nothing abnormal.

After standard dietary preparation for three days, the glucose tolerance curve was as follows (Fig. 2): fasting, 59 mg. per cent (Somogyi); one hour, 148 mg. per cent; two hours, 92 mg. per cent; two and one-half hours, 53 mg. per cent; three hours, 22 mg. per cent; three and one-half

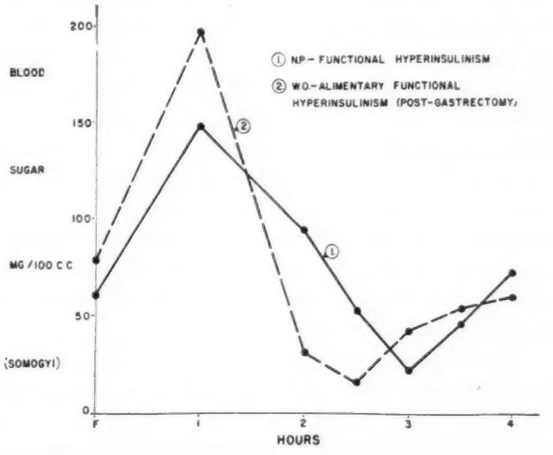


FIG. 2. Glucose tolerance curves in functional hyperinsulinism and in alimentary functional hyperinsulinism.

hours, 46 mg. per cent; four hours, 74 mg. per cent. Following the two and one-half hour sample the patient noted the onset of weakness and shakiness, which partially subsided after the third hour but persisted to some extent until she had lunch after completion of the test.

A diagnosis of functional hyperinsulinism was apparent, but in order to rule out the unlikely possibility that symptoms were caused by a functioning insuloma, the patient was fed a diet of 50 gm. protein, 50 gm. carbohydrate and 1,200 calories for three days. On this regimen she remained asymptomatic, and daily fasting blood sugar values were: before starting the diet, 64 mg. per cent; after twenty-four hours, 44 mg. per cent; after forty-eight hours, 55 mg. per cent; after seventy-two hours, 64 mg. per cent. Adherence to a therapeutic diet containing 130 gm. of protein, 75 gm. of carbohydrate and maintenance calories resulted in prompt and sustained relief of all major symptoms.

Management. Curtailment of excessive postprandial production of insulin by minimizing the postprandial rise in blood sugar eliminates the secondary hypoglycemia. Early methods of treatment helped to establish this concept. Low carbohydrate, high fat diets with frequent feedings[96] or administration of ten units of soluble insulin thirty minutes before each

meal[97] were partially effective but unwieldy and impracticable.

In 1936 experimental and clinical data were reported[98] indicating the singular advantage of a diet high in protein in the management of these patients. In the nineteen years that have ensued, the high protein, low carbohydrate diet has proved in our experience to be the most effective form of therapy for functional hyperinsulinism. This has been confirmed both clinically[68,70,72,73,78,89] and experimentally.[99] Depending upon the tolerance of the individual for protein, we prescribe diets containing 120 to 140 gm. of protein, 75 to 100 gm. of carbohydrate and maintenance calories. This is given as three meals, the protein and carbohydrate allotments being divided as equally among the meals as is practicable.[100]

Portis[8] has attempted to circumvent the chief objection to this dietary regimen, the rigid carbohydrate restriction, by eliminating only foods containing rapidly absorbed "free sugar" and relying on atropine to block the vagotonia. However the amount of atropine required (gr. $\frac{1}{200}$ to $\frac{1}{75}$ three or four times a day) often causes side-effects as troublesome as those of hypoglycemia. Secondly, we have demonstrated that the postprandial rise of blood sugar following ingestion of isoglucogenic quantities of polysaccharides is essentially the same as that produced by glucose.[101]

Despite older reports of its occasional efficacy[102,103] pancreatic resection as a therapeutic approach in functional hyperinsulinism is wrong. The only excuse for such surgery today is the uncommendable one that an erroneous diagnosis of organic hyperinsulinism was made preoperatively.

Alimentary Functional Hyperinsulinism

Recognition of this type of spontaneous hypoglycemia should present no difficulty, since it is seen only as a sequela of gastric surgery. Aside from its clinical importance, however, it warrants discussion in some detail because it clarifies several points concerning the mechanism which produces the stimulative type of spontaneous hypoglycemia.

A final figure on the incidence of clinically significant postprandial hypoglycemia after gastric surgery is difficult to establish. Evensen[77] reported its occurrence in thirteen of thirty-seven patients following gastroenterostomy, and in ten of ninety-seven patients after gastrectomy. Fifteen of Zollinger's twenty-five gastrectomized patients with postprandial gastrointestinal symptoms had symptomatic hypoglycemia, which he believes occurs more commonly than is generally realized.[80] Gilbert and Dunlop[81] established its presence in seventeen of forty-five consecutive partial gastrectomies; and over a three-year period Adlersberg[104] saw fourteen patients with the postgastrectomy hypoglycemic syndrome. Although Welbourn[82] found significant postprandial hypoglycemia in only a few of his 300 subtotally gastrectomized patients, Capper reported an incidence of 5.2 per cent in a series of 600 such patients.[82] The actual frequency of this type of symptomatic hypoglycemia is further obscured by the fact that some patients are aware of such symptoms for but a short time following surgery, despite persistence of a profound hypoglycemic dip during subsequent glucose tolerance tests.[77,82] Nevertheless, review of the over-all data creates the impression that this type of spontaneous hypoglycemia is next in importance numerically to functional hyperinsulinism. It is likely that its incidence will increase in parallel with the increasing number of gastric operations being performed.

The role of the pyloric valve in the regulation of carbohydrate metabolism may not be appreciated until one observes the result of a by-passing operation. In the normal person ingested carbohydrate is released through the pylorus in spurts. Absorption from the small intestine extends over a relatively prolonged period. In a gastrectomized individual, however, food may pour uninterruptedly through the stoma and suddenly cover a large surface of small bowel. Absorption of glucose is then excessively rapid and results in an abnormally high initial elevation of blood sugar. This is seen best in the course of an oral glucose tolerance test. (Fig. 2.) From a normal fasting blood sugar value a rapid rise to hyperglycemic levels (usually between 200 and 300 mg. per cent) occurs within one hour. Since the patient has normal islet cell function, the initial hyperglycemic phase constitutes an excessive stimulus for insulin secretion which in turn produces a very rapid fall of the blood sugar to hypoglycemic levels. Evensen[77] and others[79] have demonstrated that the same phenomenon occurs in normal persons to whom glucose is administered by intraduodenal tube.

In Figure 2 this type of response is contrasted

with that seen in the usual variety of functional hyperinsulinism. Although the postprandial hypoglycemia which occurs in both groups is presumably the result of a sudden and abnormally large release of insulin into the blood, a sharp distinction must be made between the mechanisms involved in the two situations. Functional hyperinsulinism represents an abnormal response of functionally hyper-reactive islets to the normal insulogenic stimulus, since the initial elevation of the blood sugar is within normal limits. On the other hand, alimentary functional hyperinsulinism represents the normal response of normally sensitive pancreatic islets to an abnormal insulogenic stimulus, namely, a very high initial elevation of the blood sugar level. This, then, represents a functional pancreatic response of a different type.

The clinical manifestations of alimentary functional hyperinsulinism should not be confused with the well known "dumping syndrome," which is also a sequela of gastroenterostomy or gastrectomy. When postprandial hyperosmolar jejunal contents draw fluid rapidly into the lumen and distend it,[105] symptoms of epigastric fullness, nausea, sweating, weakness and palpitation appear within a half hour after eating and subside in less than an hour.[105,106] These symptoms are not due to hypoglycemia. A period of about an hour then elapses before the onset of hypoglycemia. Hypoglycemic symptoms appear abruptly within one and a half to three hours after meals and are primarily those of hyperadrenalinemia. Occasionally, evidence of severe cerebral hypoglycemia (diplopia, headache and mental confusion) supervene; and rare instances of loss of consciousness and even convulsions have been reported.[80] Not all patients with symptoms of the "dumping syndrome" have hypoglycemic episodes.

Since this is a pure type of stimulative hypoglycemia, the fasting blood sugar is always entirely normal and prebreakfast attacks do not occur.

Illustrative Case. Patient W. O., a fifty year old white man, was admitted to University Hospital on January 26, 1954. Two years previously subtotal gastrectomy had been performed for bleeding gastric ulcer. One month postoperatively he had noted the onset of attacks of "trembly weakness" associated with sweating, dyspnea and tachycardia, which usually appeared about three hours after breakfast, but sometimes occurred also in mid-afternoon. Severe symptoms lasted but five to ten minutes, and subsided even more quickly if he ate something at the onset of an episode. Attacks had increased in frequency but not in intensity for five months prior to admission. He had never lost consciousness during a spell. Despite a good appetite he had lost 6 pounds in four months.

The patient appeared chronically ill and was malnourished. Height was 71 inches, weight 114 pounds, pulse 80 and blood pressure 110/78. Other positive findings were a transverse epigastric surgical scar; a non-tender and smooth liver edge which descended 10 cm. below the right costal margin on deep inspiration; and a palpable splenic tip 4 cm. below the left rib margin on deep inspiration.

Complete blood count and routine urinalysis were normal. Hepatogram revealed the following values: total serum bilirubin, 0.2 mg. per cent; gamma globulin, 8.2 units; thymol turbidity, 8.9 units; cephalin cholesterol flocculation, 3-plus after twenty-four hours and 4-plus after forty-eight hours; bromsulfalein retention, 1.0 per cent forty-five minutes after injection of dye; total serum cholesterol, 205 mg. per cent; total serum proteins, 6.8 per cent, with albumin, 4.5 per cent and globulin, 2.3 per cent. Barium swallow disclosed a normally functioning postgastrectomy gastroenterostomy stoma, with no evidence of obstruction or marginal ulceration.

After standard dietary preparation[91] for three days, the patient yielded the following glucose tolerance curve (Fig. 2): fasting, 77 mg. per cent (Somogyi); one hour, 194 mg. per cent; two hours, 32 mg. per cent; two and one-half hours, 16 mg. per cent; three hours, 41 mg. per cent; three and one-half hours, 54 mg. per cent; four hours, 60 mg. per cent. Just before the two-hour sample was drawn the patient noted the abrupt onset of weakness, inward trembling and sweating, with attenuation of these symptoms in about fifteen minutes. The diagnosis of alimentary functional hyperinsulinism was thus confirmed. Postprandial symptoms were abolished within three days by a diet containing 120 gm. of protein, 125 gm. of carbohydrate and maintenance calories.

Management. A medical program designed to prevent abnormally rapid intestinal absorption of glucose eliminates the initial hyperglycemia and, consequently, the secondary hyperinsulinism and hypoglycemia. Excellent results have

been obtained with the same high protein, low carbohydrate dietary regimen which is used in functional hyperinsulinism. Symptoms are well controlled on a three-feeding schedule, although some postgastrectomy patients prefer a six-meal regimen.

Organic Hyperinsulinism

The important differential diagnostic criteria which separate organic hyperinsulinism from other forms of spontaneous hypoglycemia have been outlined. (Table II.) However, a number of additional points in relation to this disease require discussion.

McQuarrie has recently delineated a syndrome which he has temporarily named "idiopathic spontaneous hypoglycemia of infancy."[51] (Table I.) This is discussed in detail later in the present paper. For integrative purposes, however, brief reference to it must be made at this point. This disease is characterized by severe fasting hypoglycemia without a demonstrable organic lesion. It occurs in infancy or early childhood and subsides spontaneously as the child grows older. In the active phase of this disturbance the clinical and laboratory findings are indistinguishable from those observed in organic hyperinsulinism. Thus it is now necessary to consider seriously the age of the patient before advising pancreatic exploration. Furthermore, since pancreatic islet cell tumors do occur below the age of five years (although this is very rare), a clear-cut differential diagnosis in this age group may be impossible by present testing methods.

Nature of the Lesion. In Howard's compilation of 264 hypoglycemic patients upon whom pancreatic surgery had been performed,[7] five were children below the age of five years. Two of them harbored an adenoma, while normal islet tissue was present in three. Critical review of the data in sixteen adults whose subtotally resected glands were thought to contain hyperplastic or hypertrophic islets, suggests that most of these cases had been instances of functional hyperinsulinism and that the rest probably harbored an undiscovered insuloma postoperatively. It is our opinion and that of others[89,90] that organic hyperinsulinism due to hyperplastic islet tissue is indeed rare in the adult.

About 9 per cent of functioning islet cell tumors are malignant, the presence of metastases being required for a diagnosis of malignancy.[5–7] No case of islet cell carcinoma has been reported below the age of eighteen.[7] Thus it would appear that in adults about 90 per cent of cases of organic hyperinsulinism are due to the presence of one or more benign, functioning islet cell adenomas. It is of some interest that over 80 per cent of islet cell adenomas (on the basis of autopsy findings) are devoid of function.[5,107]

Useful Procedures in Suspicious or Borderline Cases. As has been emphasized, a diagnosis of organic hyperinsulinism cannot be made unless unequivocal fasting hypoglycemia can be demonstrated repeatedly. In most cases this phenomenon is easily demonstrable even when the patient is ingesting a diet abundant in carbohydrate. In milder cases, however, severe restriction of carbohydrate may be necessary to prove the existence of fasting hypoglycemia. Wilder[68] advises a thirty-hour fasting period. When severe symptoms of hypoglycemia develop, requiring administration of glucose, the blood sugar level is expected to be 40 mg. per cent or less (Folin-Wu).

As the initial approach to suspicious cases we employ what we have termed a "provocative diet" for a period of three days. This diet contains 50 gm. of carbohydrate, 50 gm. of protein, and a total of 1,200 calories. The patient is hospitalized during this period and daily fasting blood sugar values are determined. If an insuloma is present the diagnosis is abundantly clear before forty-eight hours have elapsed. When diagnostic hypoglycemia has not become evident after three days on the provocative diet, the patient is fasted on the fourth day. This is followed by two hours of vigorous exercise on a stationary bicycle on the morning of the fifth day, the patient still fasting. When we have failed to demonstrate fasting hypoglycemia with the three-day provocative diet, we have failed also during the subsequent procedures. We believe, however, that the entire procedure must be carried out if one is to be certain that organic hyperinsulinism does not exist. The importance of this test or a similar one[68,108] in distinguishing functional hyperinsulinism from organic hyperinsulinism cannot be overemphasized.

The importance of the blood sugar lowering effect of exercise as a helpful diagnostic procedure in organic hyperinsulinism has been emphasized by Ford.[109] He observed that a previously symptomatic patient may have no attacks, and may even tolerate a day or more of fasting, during the tranquillity of hospital

bed rest. Prolonged delay in diagnosis, ranging from months[110] to years,[89] has been reported in patients with suspected insuloma, in which fasting blood sugar values remained above 50 mg. per cent during starvation in the hospital but in whom superimposed exercise was not employed. Nevertheless, in early or mild cases diagnostic criteria required for operation may not be demonstrable until further progression of the disease has occurred. However, if rigid diagnostic criteria are relaxed, a large number of patients who harbor no insuloma will be operated upon unnecessarily; and many of them will lose a large part of their pancreas.

Although the glucose tolerance curve is not the most important diagnostic test in organic hyperinsulinism, its value in differentiating this type of spontaneous hypoglycemia from others has been deprecated unduly. Some authors[6,20,68] seem mystified by responses which vary from low flat curves to high plateau curves in different patients and even in the same patient. We[111] have already demonstrated in insuloma patients the important alterations that can be produced in the glucose tolerance curve by changes in the antecedent diet; but another significant factor exists. Prolonged and continuous insulin secretion from islet cell tumors appears to suppress function of the normal islets.[112] The latter, however, can be restimulated to normal responsiveness by a few days of high carbohydrate feeding. In the most severe cases of organic hyperinsulinism in which normal islet function is maximally depressed, it may require a week of very high carbohydrate feeding (500 gm. a day or more) to restore normal responsiveness. The typical glucose tolerance curve can then be obtained. We have demonstrated this to be the responsible mechanism in a study of chronic exogenous hyperinsulinism in dogs[112] as well as in an insuloma patient given alloxan, the result of which was destruction of beta cells of the normal islets without any influence upon the insulin-secreting tumor.[113]

The mechanism is of more than academic interest since in hepatogenic hypoglycemia the plateau curve cannot be depressed by high carbohydrate feeding. A hypoglycemic fasting blood sugar, followed by a high plateau curve in the presence of normal liver function, does not require an attempt to produce the characteristic curve of organic hyperinsulinism by excessively high carbohydrate feeding. On the other hand, depression of the same type of curve by high carbohydrate feeding in the presence of evidence of hepatic impairment suggests that the cause of the hypoglycemia is pancreatic in origin.

Illustrative Cases. The two brief case reports which follow illustrate some of the points discussed:

Case 1. For two years prior to admission, fifty-one year old Mr. H. B. had noted progressive frequency and severity of prebreakfast mental confusion and late afternoon attacks of weakness, tremor, sweating and disorientation. He had had one convulsion before breakfast, and once had to be aroused in the morning by administration of glucose intravenously. At 4 A.M. of the first day of admission to University Hospital, he had a severe convulsion during which he sustained a fracture-dislocation of the left humerus. The fasting blood sugar drawn four hours later was 92 mg. per cent (Somogyi). That evening a closed reduction of the dislocation was performed under intravenous pentothal® anesthesia. On the standard preparatory diet, which contains 300 gm. of carbohydrate, fasting blood sugar values for the next three days were 46, 67 and 71 mg. per cent. The following day a glucose tolerance test revealed: fasting, 53 mg. per cent; one hour, 111 mg. per cent; two hours, 84 mg. per cent; two and one-half hours, 82 mg. per cent; three hours, 70 mg. per cent; three and one-half hours, 50 mg. per cent; four hours, 51 mg. per cent; four and one-half hours, 41 mg. per cent; five hours, 40 mg. per cent. The next morning the fasting blood sugar was 31 mg. per cent. Lunch was withheld to induce a short period of fasting. At 2 P.M. the blood sugar level was 33 mg. per cent and at 4 P.M. it was 27 mg. per cent. The patient exhibited obvious mental confusion, sweating and tachycardia. Orange juice relieved these symptoms promptly.

The next three daily fasting blood sugar values, while the patient continued to eat the standard preparatory diet, were 31, 36 and 38 mg. per cent. All tests of liver function gave normal values. The diagnosis of organic hyperinsulinism was now established. It is likely that failure to obtain diagnostic values during the first three days in the hospital was due to temporary alleviation of fasting hypoglycemia by the pituitary-adrenal response to the fracture.

Aqueous ACTH (40 units intramuscularly three times a day) was begun in preparation for operation. Fasting blood sugar values for the next three days were 118, 109 and 111 mg. per

cent. A benign insuloma was excised from the tail of the pancreas. The patient is now well.

Case II. When Mr. A. H., a thirty-five year old white male, was admitted to University Hospital on September 7, 1952, he stated that unless he ate two sandwiches and drank two glasses of milk just before retiring, he did not wake up in the morning. He had been in entirely good health until May, 1950, when he first noted disorientation and amnesia upon arising after sleeping late on Sunday mornings. At the onset, breakfast quickly restored normal mental lucidity. Over the following few weeks, however, the frequency and severity of prebreakfast mental confusion increased until episodes were occurring daily and persisted for an hour or more after breakfast. In another hospital, five fasting blood sugar values (Folin-Wu) ranged from 36 to 49 mg. per cent and one was 63 mg. per cent. It was noted that each morning the patient was confused, and on one of these occasions symptoms disappeared within five minutes after glucose was administered intravenously. A diagnosis of functioning islet cell adenoma was made and on July 29, 1950, the pancreas was explored. When no tumor was found, splenectomy and an estimated 80 per cent pancreatectomy were performed. Diagnosis on the excised tissue was islet cell hyperplasia. (Subsequently, Dr. C. V. Weller, University Hospital, reviewed sections of this material and reported similarly: "Increased numbers of islets of Langerhans with increase in size of some of them. Moderate hyperplasia of islet tissue").

Within a week postoperatively, symptomatic prebreakfast hypoglycemia reappeared but was less severe than before the operation. In January, 1952, a severe attack of mental confusion occurred just before lunch. This responded slowly to ingested sugar and to intravenous glucose. Thereafter, frequent afternoon episodes accompanied by sweating, weakness and tachycardia appeared about two hours after lunch. One afternoon in February, 1952, he was found unconscious in a park. He responded to an intravenous injection of glucose. No further loss of consciousness occurred, but progressive frequency of prebreakfast, early afternoon and late afternoon attacks led to extreme introspection regarding his ultimate prognosis. He entered University Hospital for further evaluation on September 7, 1952.

Physical examination revealed no abnormalities other than moderate obesity.

On the standard preparatory diet for three days, with an additional feeding of 30 gm. of carbohydrate at bedtime, fasting blood sugar levels were 40 and 30 mg. per cent (Somogyi), and the glucose tolerance test gave the following values: fasting, 31 mg. per cent; one hour, 117 mg. per cent; two hours, 205 mg. per cent; two and one-half hours, 181 mg. per cent; three hours, 137 mg. per cent; three and one-half hours, 77 mg. per cent; four hours, 55 mg. per cent; four and one-half hours, 27 mg. per cent; five hours, 36 mg. per cent. It was concluded that the patient still harbored a functioning insuloma and that exploration of the pancreatic remnant was indicated.

For three days preoperatively the patient was given 40 units of aqueous ACTH intramuscularly every eight hours. On September 15, 1952, the day of surgery, the fasting blood sugar was 73 mg. per cent. At operation it appeared at first that the tail and most of the body of the pancreas had, in fact, been removed. However, careful exploration disclosed that most of the body remained. On the surface of the body of the pancreas a reddish purple nodule 2 cm. in diameter was observed. The nodule was excised, but when the frozen section suggested possible malignancy because of invasion of the capsule, the remaining portion of the body of the pancreas was resected. This procedure proved to have been unnecessary, since the final histologic diagnosis was benign islet cell adenoma.

Moderate elevation of the fasting blood sugar persisted until ACTH was withdrawn completely on the fifth postoperative day. Carbohydrate metabolism has continued to be normal to date (three and one-half years).

Management. When the diagnostic criteria have been satisfied, prompt surgical removal of the abnormal islet cell tissue is mandatory. It arrests progression of a disease which can eventuate in (1) permanent central nervous system damage,[6,65,114,115] (2) a prolonged and irreversible episode of hypoglycemic coma, or (3) increasing obesity which complicates future surgery. The opinion that delay of surgery might permit transformation of a benign adenoma to a malignancy is no longer held.[7]

For two reasons the patient should be prepared for surgery with ACTH or hydrocortisone. The primary purpose is to elevate the blood sugar by inducing resistance to the activity of excessive quantities of insulin. Secondly, it

appears to us that use of steroids may prevent the mysterious "idiopathic hyperthermia" which caused five of the eighteen postoperative deaths in the series of cases culled from the literature by Howard.[7] All hyperpyrexic deaths occurred within four days of removal of a benign adenoma. In the past two years a solitary insuloma has been excised from four patients at University Hospital. Three of these patients had received 120 units of aqueous ACTH intramuscularly daily pre- and postoperatively and all recovered uneventfully from their surgery. The fourth patient received no ACTH or steroids. Thirty-six hours postoperatively his temperature rose suddenly to 107°F. and he expired within two hours. No explanation for the hyperthermic crisis was disclosed at autopsy. This experience was probably nothing more than a coincidence but it deserves serious thought. A number of theoretic possibilities exist to explain this phenomenon.

At laparotomy, the surgeon can now be guided by the statistical data regarding the location, size and detectability of benign adenomas. Of 274 functioning adenomas[7] the tumors were almost equally distributed in the head, body and tail. Ectopic tumors are rare and are usually contiguous with the pancreas (in the duodenal wall, in the splenic hilum or posterior to the pancreas). Functioning benign tumors are usually of small size, the diameter in 75 per cent of them ranging from 1 to 3 cm. and rarely exceeding 5 cm.[5,6] Tumors of the body and tail tend to lie near the anterior surface of the pancreas and to be visible or palpable; whereas those in the head are usually buried deeply within the parenchyma.[116,117] Adenomas are usually of firmer consistency than normal pancreatic tissue, and are therefore palpable when not visible as purplish nodules.[20] However, de Peyster[118] reports three cases of soft, non-palpable tumors which were detectable only after the excised gland had been resected.

When no tumor is discovered in the body or tail of the pancreas, the surgeon must proceed with a meticulous exploration of the head after mobilizing the second portion of the duodenum before he considers subtotal resection. This important point has been emphasized repeatedly.[20,117,119,120] The literature contains many reports of tumors later removed from the head of the pancreas when symptoms persisted following subtotal resection. Statistically, a "blind" subtotal resection should remove 62 per cent of the tumors. However, the postoperative mortality after excision of a portion of the pancreas. (14 per cent) was significantly greater than that following simple removal of an adenoma (9 per cent).[7] The surgeon's task is complicated further by the fact that multiple adenomas occur in 10 to 15 per cent of the cases.[7]

An interesting observation, which eventually may be helpful to the surgeon, was made by McMillan.[121] While operating upon a patient with organic hyperinsulinism, he obtained blood samples for glucose determination immediately before and thirty minutes following removal of suspiciously abnormal tissue; and awaited the results before closing the abdominal wound. The blood sugar rose from 131 to 258 mg. per cent. This made him reasonably certain that he had removed the adenoma. During a previous operation on the same patient there had been no such rise in blood sugar when lymphoid tissue had been removed instead of the insuloma. One might argue that the frozen section gives the same information, but in the case of multiple tumors it would not. De Peyster[118] and Dickie[122] report similar hyperglycemia responses within ninety minutes following removal of a tumor. More observations of this kind are needed.

If the patient refuses surgery or if great obesity constitutes a prohibitive surgical risk, alternative management should be attempted on a temporary basis. Hydrocortisone can then be employed in sufficient dosage to maintain normal fasting blood sugar levels. Large doses of steroid will be required, and should be used only as a temporary expedient while the patient is being convinced of the need for surgery or is being dieted down to a weight compatible with adequate pancreatic exploration. Large doses of steroids should, of course, be used to prevent frequent hypoglycemic attacks produced by metastatic islet cell carcinomas. Alloxan has been unsuccessful in controlling organic hyperinsulinism caused by either benign[113] or malignant islet cell tumors.[123,124] Administration of an extract of the adenohypophysis, which produced permanent diabetes with islet cell degeneration in dogs, intensified the hypoglycemia in two patients with organic hyperinsulinism.[125]

Hepatogenic Hypoglycemia

Proper perspective is required in assessing the role of liver disease as a cause of hypoglycemic episodes. In relation to the large total number of

patients with severe hepatocellular disease, those who exhibit symptomatic hypoglycemia are few. Nevertheless, the absolute number is probably considerably larger than is generally appreciated. This view is strengthened by reports that previously unsuspected hypoglycemia of hepatic etiology was the principal cause of symptoms in several situations in which attention had been focused upon more obvious clinical manifestations.[32,34]

Hepatogenic hypoglycemia was first recognized in patients with advanced and irreversible lesions of toxic or neoplastic nature.[22,23,25–27] Similar cases are still described.[28] Hypoglycemia as the dominant cause of symptoms in some patients with reversible hepatocellular lesions has been established.[21,24] Recent reports that profound hypoglycemia can precipitate mental torpor masquerading as "hepatic coma" in Laennec's cirrhosis[32] or as "cerebral anoxia" in the chronic passive congestion of heart failure,[34] lend credence to the view that many cases of hepatogenic hypoglycemia are not recognized.

The clinical and laboratory criteria required for a diagnosis of hepatogenic hypoglycemia have been outlined in Table II. The characteristic response to ingested glucose is demonstrated in Figure 1. Impairment of hepatic glycogenesis as well as of hepatic glycogenolysis account for the disturbance of carbohydrate metabolism in the advanced case.[21] Fortunately, these functions are maintained in the majority of patients with hepatic disease for a longer time than are many of the other functions for which tests are available. From a diagnostic point of view three elements stand out as the critical ones: (1) inability to tolerate fasting or low carbohydrate feeding without severe hypoglycemia; (2) evidence, from multiple tests, of diffuse hepatocellular disease; and (3) a plateau glucose tolerance curve not brought down by preparation with diets very high in carbohydrate. In rare instances in which organic hyperinsulinism occurs in a patient with severe hepatic disease, the differential diagnosis will be difficult indeed, if not impossible.

In severe acute hepatic lesions of infectious or toxic etiology when hypoglycemia is present, recovery of the blood sugar regulatory functions of the liver may be expected to parallel restoration of other hepatic functions.[21,32,34]

Illustrative Case. In September, 1951, I. R., a thirty-two year old housewife, noted the onset of weakness, ease of fatigue, and stabbing postprandial upper abdominal pain. Anorexia and chronic nausea developed. Jaundice appeared five weeks after the onset of symptoms, and was associated with pruritus, dark urine and clay-colored stools. X-ray examination elsewhere led to a diagnosis of obstructive gallbladder disease. At laparotomy the gallbladder was reportedly enlarged and thickened; and although it contained no stones or gravel, cholecystectomy was performed. Postoperatively the jaundice, pruritus and anorexia abated for several weeks, but all symptoms recurred with progressive intensity. Episodes of colicky right upper quadrant pain occurred, radiating to the right scapular area. Total loss of weight from the onset of illness was 20 pounds. On March 4, 1953, the patient was admitted to University Hospital.

Except for intense jaundice she appeared neither acutely nor chronically ill. The oral temperature was 98.6°F., pulse 92, blood pressure 110/70, height 67 inches and weight 168 pounds. A soft, sharp, tender liver edge was palpable 6 cm. below the right costal margin on deep inspiration. The spleen was not palpable.

The only abnormalities in routine blood and urine studies were a positive Harrison spot test for bilirubin and a moderate increase in urine urobilinogen. The stool was light brown in color. Liver function tests revealed the following values: total serum bilirubin, 37.4 mg. per cent, with one-minute direct bilirubin, 14.1 mg. per cent, thirty-minute direct bilirubin, 23.2 mg. per cent and indirect bilirubin, 14.2 mg. per cent; gamma globulin, 33.0 units; thymol turbidity, 15.7 units; cephalin cholesterol flocculation, 4-plus after both twenty-four and forty-eight hours; total serum cholesterol, 42 mg. per cent, 25 per cent of which was esterified; prothrombin concentration, 27 per cent; alkaline phosphatase, 11.8 King-Armstrong units; total serum protein, 6.1 gm. per cent, with albumin, 2.9 gm. per cent and globulin, 3.2 gm. per cent.

Strict bed rest, a diet high in protein and carbohydrate, and vitamin supplements were prescribed. On the seventh hospital day the patient complained of nausea in the morning. Consumption of food on this day was negligible. At 3:45 P.M. she noted the abrupt onset of weakness, faintness, sweating and trembling. Blood pressure was 136/66, pulse 100. A blood sample for glucose determination was obtained and 50 per cent glucose was given intravenously. The symptoms disappeared at once. The blood sugar level at the time of

symptoms was 23 mg. per cent. The following morning the fasting blood glucose was 52 mg. per cent. Two months after the hypoglycemic episode the fasting blood sugar was 83 mg. per cent. Convalescence was slow and without relapse, but two full years passed before all tests of liver cell function had returned to normal. The etiology of the profound hepatocellular damage was presumed to be viral. It is interesting to speculate, in passing, that temporary relief of the jaundice following cholecystectomy was associated with a "stress-induced" activation of the pituitary-adrenal system.

Management. In most cases dietary management is all that can be offered. The high carbohydrate, high protein diet generally prescribed in hepatocellular disease, but with the addition of a bedtime meal to shorten the longest fasting period of the day, eliminates the hypoglycemic attacks which usually occur before breakfast. In the rare instance in which liver cell damage is secondary to an active ascending biliary tract infection, cholecystectomy may result in sufficient return of hepatic function to ensure normal carbohydrate metabolism.[21]

Idiopathic Spontaneous Hypoglycemia of Infancy and Childhood

Perhaps the most interesting recent development in this field is McQuarrie's careful delineation of the most common form of spontaneous hypoglycemia encountered in early childhood.[51] Not only does his analysis explain the mystery of the many older reports of infantile hypoglycemic convulsions in the absence of a detectable organic lesion,[7,114,115] but it also affords a simple and effective substitute for subtotal pancreatectomy.

The virtually complete absence of alpha cells in the islets of two young siblings suffering from hypoglycemic attacks led McQuarrie originally to postulate a congenital deficiency of the hyperglycemic-glycogenolytic "alpha cell factor" (glucagon) as the etiologic lesion.[126] The validity of this concept has been shaken, however, by failure to find a paucity of alpha cells in pancreatic biopsies obtained from subsequent patients. Properly, McQuarrie is unwilling now to localize the primary lesion to the pancreatic islets, because of the possibility that a pituitary insulotropic principle[125] or a hypothalamic abnormality[127] may be the stimulus causing hyperinsulinism. Examination of his data leaves little doubt that this is a type of hyperinsulinism (relative or absolute) indistinguishable from that caused by islet cell tumors in adults. The hypoglycemia is of the fasting variety, but in addition the glucose tolerance test demonstates the stimulative component, namely, a sharp secondary postprandial hypoglycemia. Although the histologic appearance of the islets is usually normal, the data are highly suggestive that excessive insulin activity is present both in the fasting and in the postprandial state. A high familial incidence (siblings and cousins) is reported.

It is noteworthy that the onset of hypoglycemic manifestations varies from the first day of life to the age of five years; and that no clinical or laboratory evidence of endocrine, hepatic or gastrointestinal disease is present. Twenty-one of McQuarrie's twenty-five patients were symptomatic before the age of two years. The clinical picture is not duplicated by other types of infantile hypoglycemia. Newborn babies demonstrate moderate fasting hypoglycemia for about two weeks, but this is asymptomatic and not progressive.[51,128–130] Occasionally a baby born of a diabetic mother develops symptoms of fasting hypoglycemia,[14,51,131] but again these are transient. During infancy some children manifest a postprandial type of hypoglycemia due to overstimulation of normal islet cells by excessive ingestion of sugar (Staub-Traugott phenomenon).[51] This is a stimulative type of hypoglycemia, the fasting blood sugar remaining normal and symptoms subsiding upon relative restriction of carbohydrate.

Idiopathic infantile hypoglycemia is not a permanent condition, but one which subsides spontaneously as the child grows older. McQuarrie emphasizes the tragedy of unrecognized cases, in which permanent brain damage remains after the hypoglycemia (which could have been controlled) has disappeared.

Management. McQuarrie believes that corticotropin is the treatment of choice; that cortisone or hydrocortisone are less effective.[51] Twenty-five mg. of ACTH gel daily may be required initially, but with time as little as 2 mg. every other day has been sufficient to prevent hypoglycemia. In four such patients, discontinuation of ACTH therapy has been possible after several months without return of hypoglycemia. In view of the success of this simple regimen in a self-correcting condition, exploration of the pancreas for an islet cell tumor (very rare in this age group) should be deferred and the possibility

re-evaluated at a later date pending future developments.

Illustrative Case. Patient L. T., a Negro girl five months of age, was admitted to the Pediatrics Division of University Hospital on December 13, 1948. She had been a normal, full term baby with no evidence of birth injury. At the age of two months she began to have episodes of jerking of the head, rolling of the eyes and "blankness." Attacks occurred every two or three days, and were not associated with fever. They lasted only a few minutes and always subsided spontaneously. Episodes were never noted within an hour after feedings. The drowsy state which followed an attack disappeared more quickly if the patient was given milk or fruit juice. Before the morning feeding on the day of admission she had had an unusually severe attack. When an electroencephalogram was said to be compatible with a grand mal convulsive disorder, the patient was discharged on a regimen of phenobarbital and dilantin.

From December, 1948, until August, 1953, she was seen periodically in the Pediatrics Clinic. During this time frequent generalized seizures had occurred despite anticonvulsant therapy, and progressive mental deterioration was observed. She was readmitted on August 24, 1953, at the age of six years, following a three-day episode of diarrhea and anorexia. She had had five severe convulsions on the day of admission.

The patient was found to be comatose, with a rectal temperature of 100°F. Frequent twitching of the extremities and occasional generalized seizures occurred intermittently. A spinal fluid sugar of 4 mg. per cent and a blood sugar of 14 mg. per cent were found. After three days of an infusion of glucose, she regained consciousness. A permanent left convergent strabismus was then noted.

Fasting blood sugars ranged from 24 to 39 mg. per cent. Oral glucose tolerance test showed: fasting, 39 mg. per cent; one-half hour, 157 mg. per cent; one hour, 137 mg. per cent; two hours, 136 mg. per cent; three hours, 92 mg. per cent; four hours, 50 mg. per cent; five hours, 29 mg. per cent. The hyperglycemic response to epinephrine and a battery of liver function tests were entirely normal.

On October 16, 1953, careful exploration of the entire pancreas disclosed no adenoma. The tail and body of the pancreas, comprising approximately 70 per cent of the gland, were resected. Histologic examination revealed some increase in the number and size of the islets of Langerhans. Staining of the islets by the Gomori technic demonstrated a normal ratio of alpha and beta cells.

Hypoglycemia has not recurred. The morning after surgery the fasting blood sugar was 192 mg. per cent, two weeks later it was 126 mg. per cent, and fifteen months later it was 90 mg. per cent. However, mental retardation persists.

REMARKS UPON SOME OF THE RARER CAUSES OF SPONTANEOUS HYPOGLYCEMIA

Finally, a few additional comments are indicated upon some of the rarer causes of spontaneous hypoglycemia, which we have included in bringing up to date our older etiologic classification.[15]

1. Hypoglycemia associated with primary hypothyroidism: Two more cases[51,52] of severe hypoglycemia responding to administration of thyroid substance have been reported. We continue to believe that hypothyroidism, *per se*, is not a cause of symptomatic spontaneous hypoglycemia. Lack of function of the adenohypophysis and of the adrenals as the result of long-continued primary hypothyroidism (myxedema of the pituitary, adrenal, etc.) is the more likely explanation. Administration of thyroid repairs their responsiveness. While this would appear to be splitting hairs, it is stated in an effort to avoid cloudy concepts.

2. Hypoglycemia associated with fibromas and sarcomas: There have now been reported twelve cases of large sarcomatous or fibromatous tumors associated with a severe, fasting type of hypoglycemia.[36,61,132] Eight of these tumors were excised with prompt disappearance of hypoglycemia. Recurrence of the tumor has occurred in five, with return of hypoglycemic attacks. Two of the tumors were assayed for insulin and none was found to be present.[36,135] Nevertheless, it has been postulated[61] that these tumors secrete insulin or something akin to it. In view of the great size of these neoplasms it would seem more likely that they are consuming selectively very large amounts of glucose.

3. Hypoglycemia associated with congenital adrenal hyperplasia: In 1951, White and Sutton[60] reported the occurrence of episodes of severe hypoglycemia in a four year old female with congenital adrenal virilism. These attacks occurred

always under conditions of stress and were not associated with excessive loss of sodium. Subsequently, Wilkins[137] also observed stress-induced hypoglycemia, without abnormality of electrolyte metabolism, in a twenty-six month old male with macrogenitosomia precox. We[138] have seen the same phenomenon in a two year old girl with congenital adrenal hyperplasia. On two occasions profound hypoglycemia occurred in the course of acute infection. In this patient, however, temporary severe depletion of sodium accompanied the hypoglycemic crises. We have also observed abnormally low levels of blood sugar in two infants with this same disease, in whom the primary problem was severe loss of sodium.

It is reasonably clear now that a fundamental disturbance in congenital adrenal hyperplasia is an inability of the adrenal cortex to produce normal amounts of hydrocortisone.[139] Deficiency of the finished product in the body constitutes an abnormally and continuously great stimulus for increased production of ACTH. The adrenals become hyperplastic and produce a large amount of steroidal material other than hydrocortisone, much of which appears in the urine as 17-ketosteroids. Thus it is not surprising that under conditions of stress, ordinarily accompanied by a sharp increase in the level of hydrocortisone in the blood,[140] some patients with this disturbance manifest symptomatic hypoglycemia. Ely et al.[141] have reported that both the fasting blood sugar and the concentration of 17-hydroxycorticoids of plasma are significantly lower in these patients than in normal children of the same age.

At present hydrocortisone is the treatment of choice in the management of congenital adrenal hyperplasia. ACTH is contraindicated. It intensifies the abnormalities which characterize the condition.

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Clinico-pathologic Conference

Jaundice and Ascites with Recovery for Two Years; Recurrence of Jaundice, with Abdominal Pain, Hematemesis and Azotemia

STENOGRAPHIC reports, edited by Albert I. Mendeloff, M.D. and David E. Smith, M.D., of weekly clinico-pathologic conferences held in the Barnes and Wohl Hospitals, are published in each issue of the Journal. These conferences are participated in jointly by members of the Departments of Internal Medicine and Pathology of the Washington University School of Medicine and by Junior and Senior medical students.

A FIFTY-NINE year old white male bus driver (No. 241074) entered the Barnes Hospital for the first time on July 31, 1954, with a chief complaint of jaundice of three weeks' duration.

For the past five or six years the patient had noted occasional mild epigastric discomfort associated with bloating following meals. About four or five years prior to admission he suffered the onset of intermittent right upper quadrant throbbing pain, particularly postprandially, which was aggravated by eating pork or cabbage. Approximately two years prior to admission the patient noted an increase in the severity of this discomfort, at which time he had the onset of non-pruritic jaundice and an increase in the girth of his abdomen, associated with anorexia, occasional vomiting and ankle edema. He was hospitalized elsewhere for fifty-five days, during which time five paracenteses were performed, with removal of 4 to 5 quarts of ascitic fluid each time. His jaundice, ankle edema and ascites gradually disappeared. His appetite improved and he returned to his job. He felt well until approximately five weeks prior to this admission; while cutting weeds he became very fatigued and noted again the onset of right upper quadrant pain, this time radiating around the right flank and across the abdomen. This pain subsequently occurred following meals. He had a gradual decrease in his appetite with some increase in abdominal bloating and flatulance. He also began to have occasional vomiting, particularly in the morning on arising. Three weeks prior to admission the patient noted the onset of jaundice associated with dark urine, light stools, a bad taste in his mouth, increasing weakness, an increase in the girth of his abdomen and more frequent vomiting during the day.

Prior to two years before admission the patient ingested alcohol only rarely on social occasions. He denied drinking alcohol at all for two years prior to admission. There had been no known exposure to hepatotoxic agents. He had lost a total of 10 pounds during the previous six weeks. His diet was not described in detail but was stated to have been "adequate."

Physical examination on admission revealed the patient's temperature to be 37°C.; pulse, 80; respirations, 16; and blood pressure, 130/80. The patient was a well developed man appearing chronically ill and mildly jaundiced. There were several arteriolar spiders on the upper trunk, but no palmar erythema. There were a few shotty inguinal lymph nodes. The sclerae were icteric, the pupils reacted to light and accommodation, and extraocular movements were intact. The eyegrounds revealed slight increase in the light reflex with some questionable temporal pallor. Examination of the ears, nose, mouth and throat was not remarkable. There was moderate increase in the anteroposterior diameter of the thorax. Examination of the lungs revealed hyperresonance on percussion with a few coarse rhonchi over the left chest anteriorly on auscultation; no rales were heard. The left

border of cardiac dullness was encountered 8 cm. from the mid-sternal line in the fifth intercostal space. The heart sounds were of good quality, no murmurs were heard, and there was a normal sinus rhythm. The abdomen was slightly protuberant; there was some bulging of the flanks and shifting dullness, but no fluid wave. There was poorly defined tenderness in the right upper quadrant. Liver, kidneys and spleen were not palpable. There was a readily reducible, left, indirect, inguinal hernia. There was a trace of pitting edema of both ankles. Rectal examination revealed a firm prostate which was two or three times normal size, was not tender and contained no nodules. No hemorrhoids were noted. The remainder of the physical examination was not remarkable.

The past history disclosed that in 1923 the patient had had pneumonia. Since then he had noted asthmatic attacks usually in the fall and the winter. One brother had asthma.

Laboratory data on admission were as follows: hemoglobin, 12.1 gm. per cent; white blood count, 6,800 per cu. mm.; differential: basophils, 1 per cent; segmented forms, 69 per cent; lymphocytes, 30 per cent. Urinalysis: pH, 5.5; protein, negative; sugar, negative; microscopic examination: amorphous urates, 4 plus; bacteria, 2 plus. Stool: guaiac-negative. Serologic test for syphilis: negative. Blood chemical determinations were as follows: non-protein nitrogen, 15 mg. per cent; fasting blood sugar, 55 mg. per cent; sodium, 137.6 mEq./L.; potassium, 4.4 mEq./L.; chloride, 100 mEq./L.; carbon dioxide combining power, 28.2 mM/L.; cephalin cholesterol flocculation, 4 plus; thymol turbidity, 38.6 units; total bilirubin, 6 mg. per cent; one minute fraction, 2.4 mg. per cent; albumin, 3 gm. per cent; globulin, 6.2 gm. per cent; cholesterol, 167 mg. per cent; amylase, 107 Somogyi units; prothrombin concentration, 22 per cent of normal; alkaline phosphatase, 5.8 Bodansky units; bromsulfalein retention, 64.5 per cent at the end of forty-five minutes. Electrocardiogram: within normal limits. Roentgenogram of the chest: minimal infiltrate in the left upper lobe which was interpreted as representing a questionable fibrotic tuberculous lesion; hypertrophic osteoarthritis of the dorsal spine; elongation of the aorta. Complete gastrointestinal series: within normal limits. Gallbladder series: non-visualization of the gallbladder. Sputum culture: a heavy growth of neisseria and a moderate growth of beta-hemolytic streptococci.

The patient's hospital course was uneventful until the sixth hospital day, at which time he began to complain of severe aching pain in the right flank, radiating inferiorly to the pubis and questionably to the right side of the scrotum. He denied dysuria, urinary frequency or urgency. At that time he manifested extreme tenderness in the right costovertebral angle with radiation of the tenderness anteriorly around the right flank, and his temperature spiked to 38.5°C. Urinalysis was as follows: pH, 4.5; protein, negative; sugar, negative; microscopic examination: mucus, 3 plus; 30 to 35 white blood cells per high power field, moderate number of epithelial cells, rare red blood cells, rare white blood cell casts. A urine culture grew a few colonies of Staphylococcus albus and Staphylococcus aureus, and a moderate growth of beta-hemolytic streptococci. He was given tetracycline, 250 mg. orally every six hours. However, this dose was changed to 200 mg. intramuscularly four times a day because of vomiting which began after three oral doses of the medication; the intramuscular drug was continued throughout the remainder of his hospital stay. By the following day he had been given three doses of atropine, 0.4 mg. each dose. His discomfort had decreased but was still present. His abdomen was distended and there was tenderness in the epigastrium and the right upper quadrant. A rectal examination at that time was not remarkable; there were no feces in the rectal ampulla. The white blood count on the seventh hospital day was 14,750, the differential count comprising myelocytes, 6 per cent; metamyelocytes, 19 per cent; band forms, 50 per cent; segmented forms, 20 per cent; lymphocytes, 4 per cent; monocytes, 1 per cent. Slight hypochromasia of the red blood cells with adequate platelets was noted and two atypical lymphocytes were seen. Roentgenograms of the chest and abdomen: discoid atelectasis at the base of the right lung, and ascites; because of the absence of gas in the rectum and large bowel it was believed that a very early small bowel obstruction could not be excluded on the basis of this roentgen examination. The patient continued to vomit and was maintained on parenteral fluids. On the morning of the eighth hospital day retrograde pyelograms were taken; these were within normal limits. The patient's emesis became coffee-ground in quality. On the afternoon following the retro-

grade pylography the patient's blood pressure was found to be 74/40 with a pulse rate of 120. An electrocardiogram showed no change. He was given vasoxyl,® 20 mg. intramuscularly, with subsequent rise in blood pressure to approximately 100/60. The patient was then placed on an intravenous drip of nor-epinephrine in the amount of 4 mg./L.

The patient's condition rapidly deteriorated. The serum non-protein nitrogen increased progressively to a high of 174 mg. per cent on the fourteenth hospital day at which time the serum potassium was at its height, 7.4 mEq./L. Despite electrolyte and fluid replacement his serum sodium remained low, in the range of 125.8 mEq./L. to 132.1 mEq./L. He was maintained on almost constant gastric suction. Intravenous nor-epinephrine was continued until the eleventh hospital day, but it had to be reinstituted on the thirteenth day because of a gradual fall in the blood pressure in the previous twelve hours to a low of 75/35. The patient's jaundice became more intense His urine output decreased from 500 ml. on the seventh hospital day to only 100 ml. on the thirteenth hospital day. He was given large doses of parenteral vitamins in addition to sodium glutamate, 23 gm. per day, for three days beginning on the eleventh hospital day. The prothrombin concentration fell to 15 per cent of normal despite administration of parenteral vitamin K, 20 mg. each day, beginning on the fifth hospital day. Fresh ecchymoses at pressure sites were noted on the eleventh hospital day. The patient became intermittently irrational, and died quietly on August 13, 1954.

CLINICAL DISCUSSION

DR. EDWARD REINHARD: I would like to start the conference by having Dr. Elliott show us the x-ray films.

DR. GLADDEN ELLIOTT: The first examination was of the chest, and one of the few positive findings suggested was a questionable infiltrate of the second anterior interspace representing minimal fibrotic pulmonary tuberculosis. The remainder of the chest was normal. A gastrointestinal series was negative, and a retrograde pyelogram on August 7th showed normal collecting systems bilaterally. At that time the patient had a rather marked degree of ascites.

DR. REINHARD: This patient, a fifty-nine year old bus driver, had only one admission to the Barnes Hospital, and he died two weeks after this one admission. He was not an alcoholic; his diet is stated to have been adequate, although a detailed description was not available. About six years prior to this admission he had noted occasional mild epigastric discomfort associated with postprandial bloating. Two years prior to admission abdominal pain developed. The intern's note stated that this was a right upper quadrant throbbing pain; the assistant resident's note described this as a right lower quadrant pain which was constant, dull and aching in character. Two years prior to admission an increase in severity of this pain developed, associated with non-pruritic jaundice, an increase in the girth of his abdomen, and anorexia, occasional vomiting and ankle edema. He was hospitalized for two months, during which period five paracenteses were performed, each one yielding from 4 to 5 quarts of ascitic fluid. At the end of this two months of hospitalization his jaundice had subsided, his ankle edema had cleared up, his ascites had disappeared and he was asymptomatic. As far as we know he was entirely well so far as any residual evidence or clinical symptoms were concerned. He returned to work following this and remained well for a period of two years. In June, 1954, after two years of freedom from any symptoms, symptoms referable to his terminal illness began to develop. This was five weeks prior to his admission to the Barnes Hospital. Dr. Shank, this patient was not seen during the two-year interval when he was asymptomatic, so we have inadequate data about him during this period. If this patient had come to see you in June, before any of his terminal symptoms developed, saying he had felt perfectly well for two years but giving you this interesting history, how would you have interpreted this past story?

DR. ROBERT E. SHANK: Under the conditions that you have outlined I would have wanted to review the history very carefully and obtain a little more data than our protocol contains. With the information that we have available to us in this synopsis of his history, it seems to me that there are several possibilities, each difficult to assess. One of these possibilities is that cirrhosis had developed at the time of his final illness, either on the basis of a nutritional deficiency or as the result of previous hepatitis. For that reason I would have liked to know what this man's dietary intake was five or six years ago rather than in more recent months.

DR. REINHARD: I am sure we both agree that

the dietary history available was totally inadequate.

DR. SHANK: Another possibility is that this man may have previously had an acute illness involving his liver, the most likely type being viral hepatitis. If that were true, hepatitis would have been occurring in a man of relatively advanced age; it is a much more common disease in earlier life. On the other hand, it does occur in older age groups and is frequently associated with a prognosis that has to be more guarded. In other words, the man would have been more likely to have had a severe course, because he was older than fifty at the time of onset. If he had had acute hepatitis at that time, we would have to postulate that the course of this acute illness was not the usual one, going on to complete cure, but that he had had a period of prolonged convalescence with the persistence of some symptoms and the evolution of a chronic lesion following his acute hepatitis. Regardless of the initial type of liver disease he could have had remissions and exacerbations. In the course of his illness this man undoubtedly had a rather long period of remission of his disease, but this does not help us decide what was the initial event in his illness. Something had happened at the time of his final illness to cause an exacerbation of his disease.

DR. REINHARD: Would you like to favor one or the other of these types of chronic liver disease?

DR. SHANK: If you will put it in the category of a guess, I will make one. When first seen here this man did not have a palpable liver or spleen. If his primary disease had been portal cirrhosis induced by dietary deficiency, his liver probably would have been palpable and with this course his spleen also might have been palpable. However, there are instances when significant hepatomegaly is absent in portal cirrhosis. If, on the other hand, he had had postnecrotic cirrhosis, it would have been more likely that his liver would not have been palpable when he was seen here. On that basis, then, we could lean a little more to the initial diagnosis of acute hepatitis progressing to postnecrotic cirrhosis. I would like to stress that the initial disease would not necessarily have had to be viral hepatitis. It could have been acute liver damage of some other type, for example, that due to hepatotoxins.

DR. REINHARD: Dr. Karl, will you comment on this fact: this patient has ascites requiring five paracenteses in a period of two months; the ascites then cleared up and he required no further taps for a period of two years. Do you think this constitutes very convincing evidence against either type of cirrhosis?

DR. MICHAEL M. KARL: I think it would not provide evidence against either type. One must remember that in the production of ascites in liver disease there are many factors involved other than portal hypertension. These include an excess of antidiuretic substance, sodium retention presumably on a hormonal basis, changes in the levels of the serum protein, and changes in the permeability of the capillaries. All of these are conditions in which reversible factors are operating. These might well change in the course of either of these two conditions under consideration.

DR. REINHARD: Have you seen this?

DR. KARL: Yes, I have.

DR. REINHARD: Dr. Shank, how often does a patient have ascites which then clears up? Is this very common?

DR SHANK: This is not at all uncommon in carefully managed patients.

DR. REINHARD: Many different varieties of chronic hepatitis have been described and many names have been applied to differentiate the variations in the clinical picture following acute hepatitis. One type is the benign condition called in the literature posthepatitis bilirubinemia which may be persistent or intermittent. A second category is acute infectious hepatitis with "apparent" recovery, "apparent" because these patients end up with advanced cirrhosis. Therefore it would appear that during this period of freedom from any symptoms or manifestation of disease, there must have been some latent process which caused progressive damage to the liver. The third category of chronic active infectious hepatitis may be of various types. It may be characterized by continuous or recurrent jaundice, or by persistent symptoms and laboratory evidence of hepatic dysfunction. Jaundice may be absent but the patient may have various vague symptoms of anorexia, bloating and nervousness without any physical signs or laboratory evidence of hepatic dysfunction. These patients are often diagnosed as having psychoneurosis. Indeed, many of them may be patients with psychoneurosis who had active hepatitis in the past and whose exacerbation of psychoneurosis dates from the acute attack of hepatitis. The fourth category has been called chronic inactive infectious hepatitis. This may again be with or without

jaundice. This is a rather vague category, hard to distinguish from the other cases of chronic active infectious hepatitis. In many instances there may have been very little to indicate actual activity of the disease process. Dr. Mendeloff, would you care to tell me first whether you think this patient had primarily hepatitis or nutritional liver disease?

DR. ALBERT I. MENDELOFF: At the time this patient entered this hospital he presented the signs of chronic liver disease, most probably cirrhosis. When one tries to differentiate among the specific types of cirrhosis in a case in which the history is as unrevealing as this one was, one has to use a number of other findings, either laboratory or physical, which statistically are more often associated with one type than another. As Dr. Shank pointed out, in this case the liver was not palpable, nor was the spleen. The patient had a few spider angiomas, was moderately jaundiced, and had some fluid in his abdomen. The fact that his liver and spleen were not palpable is, statistically, most often associated with the postnecrotic form of chronic liver disease, whether postnecrotic scarring alone or whether postnecrotic cirrhosis, the more active form. The laboratory data tend to confirm this again from a statistical point of view. They reveal several features which are more often associated with the postnecrotic type of cirrhosis than with a diffuse cirrhosis. First the serum globulin was 6.2 gm. per cent. This is an extremely high value for either disease, but values over 5 are far more common in the form of disease which we call postnecrotic cirrhosis. Second, the normal alkaline phosphatase is in keeping with postnecrotic cirrhosis. The very high thymol turbidity and a very high cephalin cholesterol flocculation are not very helpful in differentiating the two types. I do not believe they help us one way or the other. I would say that both clinical findings and the laboratory data tend to favor postnecrotic cirrhosis in this case although, as everyone knows, none of these points is conclusive.

DR. REINHARD: After this asymptomatic two-year period, on June 12, 1954 (five weeks before death), the patient became very fatigued and noted the occurrence of right upper quadrant pain while cutting weeds on a friend's farm. This pain radiated around the right flank and down to the lower abdomen. Subsequent recurrences of this pain occurred and seemed to come on more often after meals. A progressive increase in anorexia, bloating and edema developed. He began to have occasional vomiting spells, particularly on arising in the morning. Shortly thereafter he noted the onset of jaundice. This was again without pruritus. He had dark urine and a bad taste in his mouth, weakness became steadily more marked, and there was an increase in the size of his abdomen. More frequent vomiting occurred during the day. The day before admission his vomitus contained a small amount of blood for the first time. On the day of admission his stool was the color of light cream for the first time. During the six weeks prior to his admission to the hospital he lost 10 pounds. The patient had had no chills, he did not think he had had any fever, and upon admission to the hospital he did not have any fever. On physical examination his temperature, pulse and respiration were normal. The patient was mildly jaundiced. There were several arterial spiders on the upper trunk. He had no palmar erythema. The scleras were icteric. The abdomen was slightly protuberant. There was some bulge in the flanks and shifting dullness, but no fluid wave was noted. The liver, spleen and kidneys were reported by several investigators to be not palpable. There was a trace of pitting edema of both ankles. He had no hemorrhoids. Dr. Kenamore, this was your patient. When you saw him at this time, what diagnoses did you consider as the cause of the rather sudden onset of acute symptoms?

DR. BRUCE KENAMORE: When I first saw this man, about two or three days before he entered the hospital, I thought he either had had an exacerbation of cirrhosis which resulted from acute hepatitis with prolonged course occurring two years before, or, lacking any laboratory data at the time I first saw him, that he had obstructive jaundice. He was obviously ill and in need of hospitalization and nothing more was done in the way of history or physical examination until he was admitted to the hospital. Those were the two considerations in my mind at the time of admission.

DR. REINHARD: On admission he had mild anemia, hypoglycemia, a low serum cholesterol, a prolonged prothrombin time, markedly elevated cephalin cholesterol flocculation and thymol turbidity, profound bromsulfalein retention, and a serum bilirubin markedly elevated in both direct and indirect fractions. Dr. Recant, do these findings help us any in determining what the nature of this insult to the liver was?

DR. LILLIAN RECANT: The only conclusion one could reach from these findings is to say that there was no evidence of any obstructive phenomenon, and that there had been severe hepatocellular damage.

DR. REINHARD: On the sixth hospital day the patient began to have severe aching pain in his right flank. This radiated down to the genitalia. There was extreme costovertebral angle tenderness. He had fever at this time, 20 to 30 white cells in the urine, and very few red cells. Urine culture grew out beta-hemolytic streptococcus and only a few straphylococci. The day after these events he had a white blood cell count of 14,700, with a very striking shift to the left. Dr. Harford, was this a separate urinary tract infection, or was this a renal disease due to or associated with his liver disease?

DR. CARL G. HARFORD: This probably was a urinary tract infection.

DR. REINHARD: What organism would you have suspected here?

DR. HARFORD: The laboratory isolated a streptococcus that gave beta-hemolysis. One would not expect, it seems to me, to have urinary infection due to group A streptococci; however, there are some enterococci encountered in the urine which would also give beta-hemolysis, so I imagine they were the organisms isolated.

DR. REINHARD: I have never seen so marked a shift to the left with a total white cell count of only 14,000 in the presence of a hemolytic streptococcal infection. I am a little disturbed by this. I have seen this more often in association with profound necrotic disease—advanced carcinoma with profound necrosis or, perhaps, with profound liver necrosis. Does this white blood cell count disturb you?

DR. HARFORD: Yes, it does disturb me. All the rest of the circumstances are such as to indicate that any urinary tract infection which was present would probably have been fairly promptly controlled by the medication given.

DR. REINHARD: This patient began vomiting continuously thereafter. The day after the onset of these acute symptoms his abdomen became distended. A small bowel obstruction was suspected by at least one observer. On the eighth hospital day, two days after the onset of acute symptoms of fever and the like, the patient vomited coffee ground material. That same day, in spite of the fact that his non-protein nitrogen concentration was 62 mg. per cent, bilateral retrograde pyelography was performed. The following day the patient went into shock which was treated with vasoxyl and norepinephrine. Jaundice became progressively more intense and his urinary output steadily decreased, finally reaching anuric levels. During the last two days of his illness his blood pressure fluctuated between 80 and 105 systolic and 50 and 55 diastolic. On the day of death the sodium was low and the potassium was high. Dr. Sherry, what kind of kidney disease do you think this patient had, and would you comment on these terminal events?

DR. SOL SHERRY: About five, six or seven days after some patients have had a very severe acute hepatic insult, they will suddenly go into acute renal insufficiency. I think that the pathologist will show us evidence of acute tubular necrosis; I believe this case was an example of the hepatorenal syndrome. The terminal events might almost suggest that there had been some adrenal insufficiency of a physiologic nature as well.

DR. REINHARD: Do you think that taking the retrograde pyelograms when the patient was azotemic was ill-advised, or did this have nothing to do with the terminal events?

DR. SHERRY: I doubt that it had anything to do with the terminal events.

DR. REINHARD: Dr. Harrington, would you discuss this patient's terminal bleeding difficulties? Just before he died bleeding from his gastrointestinal tract developed which may or may not have been due to a localized gastrointestinal lesion. He also certainly had a blood dyscrasia of some sort because he had a great many spontaneous ecchymoses occurring during the last few days of life. We all know the patient had a profoundly low prothrombin concentration in his blood. Are there any other mechanisms for the bleeding that we would have had to consider?

DR. WILLIAM HARRINGTON: Yes, in the terminal stages of liver disease many abnormalities may be noted. Deficiency of prothrombin, accelerator globulin and convertin all contribute to prolongation of the one-stage determination of prothrombin time. In addition, hypofibrinogenemia can occur, although it is an unusual cause for generalized bleeding in cirrhosis. Nevertheless, the fibrinogen is of a poor quality, "less reactive," and possibly related to the low grade proteolytic activity seen in the plasma of these patients. Some have imputed a deficiency of "thrombin accelerator" to the plasma. Lastly, thrombocytopenia is

frequently a factor, although this patient apparently did not have a significant depression of his platelet levels.

DR. MENDELOFF: In general, when a person with stable chronic liver disease suddenly fails, one suspects either that he is having episodes of hepatic necrosis, or else hepatoma has developed. This latter development is often ushered in by an episode of pain in the general area of the liver, and the liver need not be enlarged. At the same time this cancer may also be associated with complications such as thromboses in the portal system which might well have caused the leukemoid reaction in his blood, the abdominal distention and the gastrointestinal hemorrhages, even though the spleen was not noted to be palpable. He did also have a gallbladder which was not visualized by x-ray; this may have been due to the inability of the liver to excrete the dye, but there is a possibility that acute cholecystitis or acute pancreatitis developed, which might have accounted for his terminal episode.

DR. W. BARRY WOOD, JR.: Could thrombi in the hepatic vein have gotten into the inferior vena cava and involved the renal vein, to explain this very sudden renal insufficiency, or is that unlikely?

DR. MENDELOFF: That has been described, Dr. Wood, but I should have expected him to show hematuria rather than pyuria alone.

DR. REINHARD: If this was portal thrombosis, should not the liver have enlarged terminally, or did he die too soon for that?

DR. MENDELOFF: If the thromboses were in his portal system, they need not have affected the size of the liver.

DR. REINHARD: The clinical diagnoses of the house staff were: (1) Laennec's cirrhosis, (2) acute hepatic necrosis, (3) obstructive emphysema, and (4) acute pyelonephritis, right.

PATHOLOGIC DISCUSSION

DR. DANIEL L. ROSENSTEIN: The body of this man was markedly icteric; there were spider hemangiomas in the skin over the upper thorax and shoulders, and petechiae along the costal margins and about the umbilicus. The testes were atrophic and there was moderate subcutaneous edema about the ankles. The peritoneal cavity contained 5,000 ml. of clear ascitic fluid, and venous varicositis were apparent in the omentum and on the inferior surface of the diaphragm. On cutting through the esophagus some intramural varices were exposed, but these did not distort the mucosa and there was no evidence of any rupture. In the remainder of the gastrointestinal tract there were many petechiae throughout the mucosa, and the contents of the lumen consisted mostly of blood-tinged mucus. A few superficial erosions were present in the fundus of the stomach.

A section of the liver is illustrated in Figure 1. This organ was of decreased size. It weighed 1,160 gm. and was rather soft and flabby. The capsular surface presented numerous rather small and widely separated nodules. On the surfaces exposed by incision there were two types of nodules: a small rust-brown nodule that bulged above the surface, and larger and more irregular nodules which were yellow and soft and had a hyperemic peripheral zone. Between these nodules there were confluent bands of firm, yellow-gray, rather translucent fibrous tissue. The spleen had the appearance of chronic passive congestion and was slightly enlarged to a weight of 320 gm.

The heart was not remarkable except for petechiae and ecchymoses present both in the endocardium and in the epicardium. Petechiae were also scattered over both the visceral and parietal pleurae. The lower lobes of the lungs were atelectatic and slightly congested. The kidneys were scarred and icteric, but their cortices showed no evidence of swelling. The capsular surfaces presented several small cortical cysts and were moderately irregular.

DR. W. STANLEY HARTROFT: The history of this patient, the clinical discussion and the gross findings at autopsy have all served to focus our interest on the liver. Microscopically it is composed of nodules of parenchyma widely separated by bands of a collapsed, rather loosely arranged stroma. (Fig. 2.) Recent cellular necrosis has occurred throughout many of the nodules, with but small zones of surviving parenchyma at their edges in some instances. In the latter regions there is evidence of abortive attempts at regeneration in the form of pseudocholangioles. (Fig. 3.) Hemorrhage is present throughout the necrotic centers of the nodules. Where necrosis has not obscured the picture, it is evident that in many of the nodules portal triads and radicals of central veins are present. Other nodules represent only fragments of liver lobules. Occasional parenchymal cells with more than one nuclei are encountered throughout, but regenerating liver plates, two cells in thickness, are rarely encountered. In the scarred

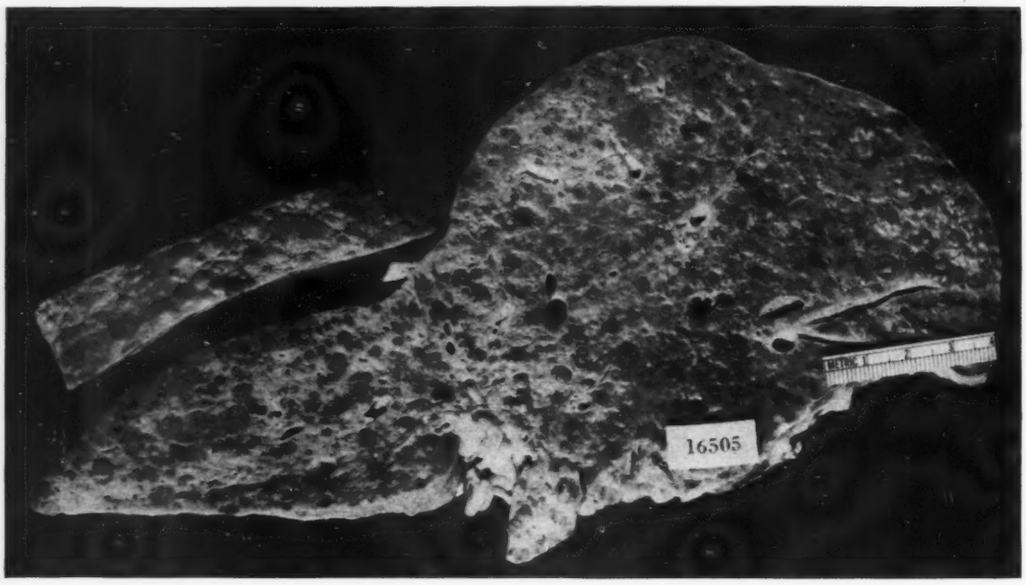


FIG. 1. Sections through the hilum and showing the capsule of the liver. There is extensive interstitial scarring with slightly irregular nodules of surviving parenchyma. The darker nodules are hemorrhagic and necrotic.

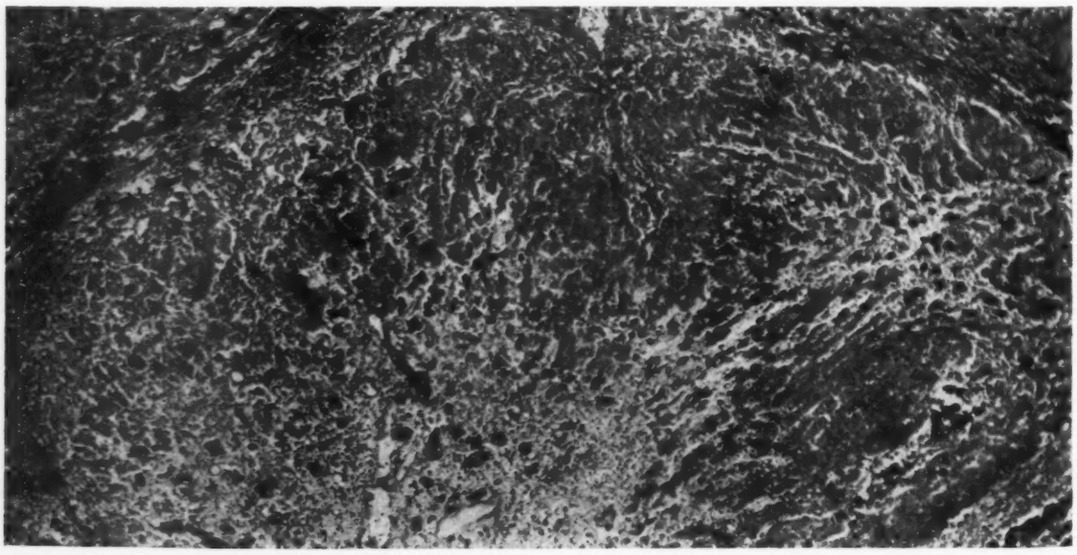
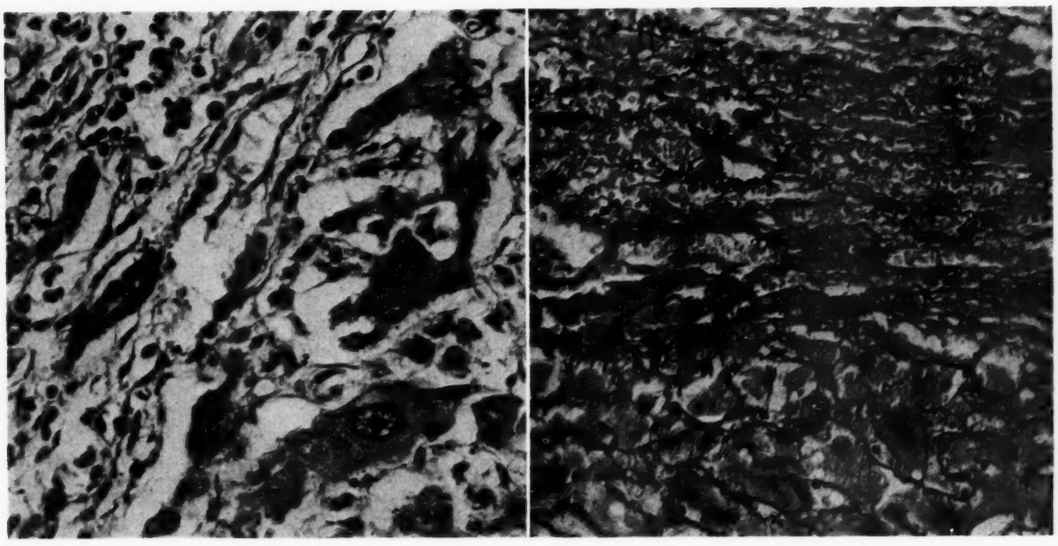


FIG. 2. The area between three nodules in the liver showing the rather loose fibrous scar infiltrated with lymphocytes and mononuclear cells. The parenchymatous nodules contain several portal units and central veins and variable amounts of necrosis.

areas (Fig. 3) generous numbers of mononuclear cells and lymphocytes are encountered. The other cellular constituents of the scarred areas consist of isolated liver cells, cholangioles and blood vessels. By appropriate technics surprisingly little collagen can be demonstrated. Silver stains (Fig. 4), however, reveal that the normal reticulin content of the liver has persisted in the scarred areas, becoming only slightly compressed and contracted, so that the fibers are coarser than usual. Lamination of the reticular fibers is not advanced, still another indication that the adjacent nodules of parenchyma have undergone but little regeneration. Bile pigment is present in many liver cells, and both cholangioles and bile ducts contain plugs of inspissated bile. In this liver, therefore, the parenchymal nodules are multilobular in many instances; many have undergone recent acute necrosis with hemorrhage; and the scarred areas consist chiefly of



3 4

FIG. 3. The edge of a nodule in the liver at high magnification. Pseudocholangioles and lymphocytes are present in the loose scar tissue surrounding the irregular hepatic cells which are arranged in single cell plates.

FIG. 4. Reticulin impregnation demonstrating the slightly coarsened and compressed fibers in the scarred areas in the liver. This change is not nearly as striking as is seen in true cirrhosis.

collapsed, but only slightly compressed reticulin, mononuclear cells, pseudocholangioles and remnants of liver plates. Fat is almost completely absent throughout all sections. The microscopic findings therefore suggest postnecrotic scarring, with a recently superimposed necrosis.

In microscopic sections of the esophagus moderately dilated submucosal veins without evidence of rupture are encountered. In the testes the tubules are atrophic and interstitial cells have disappeared almost entirely. Sections of the kidney reveal evidence of chronic pyelonephritis with considerable destruction of parenchyma. Tubular necrosis is absent.

Finally, in the pancreas portions of the acinous tissue and adjacent fatty tissue appear necrotic. Polymorphonuclear inflammatory reaction is prominent in these areas. In microsections of the heart and the gastrointestinal tract the petechiae seen grossly are visualized, but other significant abnormalities are not encountered.

The gross and microscopic findings revealed at autopsy indicate that the liver had suffered a severe degree of destruction. The histologic features suggest that death of liver cells occurred in at least two distinct episodes. The scarred nodular pattern, absence of fat or evidence to indicate abnormal fat previous to death suggest that the scarring may have been caused by a previous attack of viral hepatitis. The second episode, consisting of acute necrosis in the surviving nodules of parenchyma, is of more recent occurrence, possibly occurring on a circulatory basis. The morphologic evidence fails to suggest that hepatotoxins or nutritional deficiencies were responsible for the production of hepatic damage. It is possible that the development of terminal acute pancreatitis acted as an accessory factor responsible for the final episode of acute hepatic destruction.

Final anatomic diagnoses: Postnecrotic scarring of the liver with acute necrosis of persistent parenchyma; acute pancreatitis with fat necrosis; petechiae and ecchymoses in the gastrointestinal tract, pericardium, urinary tract and skin.

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Case Report

Subacute Bacterial Endocarditis Due to Listeria Monocytogenes*

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MEDICAL writings now contain many references to Listeria infection in man. A recent review[1] tabulated 147 cases of reported human infection. Forty-five of these cases were infections of the meninges; none was thought to involve the endocardium. In this same review thirty-six additional cases (nine meningitis, no subacute bacterial endocarditis) were listed which were possibly due to Listeria.

Other reviews[2,3] stress meningitis as being the most frequent form of human Listeria infection. The possible relationship of Listeria to infectious mononucleosis, a human illness in which isolation of Listeria has been reported, was thoroughly discussed by Girard and Murray.[2] No mention was made of subacute bacterial endocarditis due to Listeria in any of these reviews.

In writings dealing with bacterial endocarditis Listeria was not included among the listed etiologic agents.[4–6] So far as we have been able to ascertain, this is the first case of subacute bacterial endocarditis due to Listeria monocytogenes to be reported. Moreover, it is one of the rare instances of human Listeria infection in which significant levels of Listeria agglutinins have been demonstrated.

Adequate descriptions of the history of Listeria, of its bacteriology and epidemiology are contained in any of the reviews previously referred to. Writings pertinent to the immunologic aspects of listerosis are reviewed subsequently.

CASE REPORT

On March 21, 1954, a forty-two year old white man was admitted to the private Medical Service of the Grace-New Haven Community Hospital for study of an illness suspected of being subacute bacterial endocarditis. Three years prior to entry, when he first became the patient of one of the authors (H. M. C.), he was found to have rheumatic heart disease with both mitral and aortic valvular involvement. He could not recall having had rheumatic fever or any of its equivalents although three years prior to this initial examination he had a sore throat with cervical node enlargement. The patient was not seen again until one year prior to admission when he complained of easy fatigability and mild exertional dyspnea. There was no evidence of cardiac failure and the cardiac murmurs were unchanged. An electrocardiogram was normal; by x-ray examination after barium swallow there was slight enlargement of the left auricle. He weighed 203 pounds and was advised to reduce. With restriction of caloric intake, amphetamine and methylcellulose, his weight dropped to 190 pounds, and his symptoms subsided.

In May, 1953, because of persistent pain in his jaws, the patient consulted his dentist. Severe periodontoclasia was discovered, and on June 19, 1953, the patient's remaining twenty-eight teeth were extracted. On the day before, the day of, and the day after surgery, the patient was given 600,000 units aqueous procaine penicillin G intramuscularly. No chills, fever or malaise obtained. Artificial dentures were fitted but were unsatisfactory, for the patient could not chew properly with them. On July 27, 1953, a retained tooth fragment was excised and several sutures were required to close the operative wound. No penicillin was given during this procedure. Four months after this surgery (four months prior to entering the hospital) the patient

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began to have "stiffness and weakness" of both knees. This was most severe on arising in the morning and wore off by evening. Concomitantly, a gradual decrease in "drive and energy" set in. Although the knee pains spontaneously disappeared, the lack of energy grew more prominent as time passed. This he ascribed to poor food intake caused by pain from the false teeth.

On March 6, 1954, he first sought medical attention because of recurring chills and fever. About three weeks before this visit he had an upper respiratory infection manifested by coryza and a non-productive cough. Ten days before, he had a sudden shaking chill, lasting about thirty minutes, followed by drenching sweats and profound weakness. The following day he felt better and went to work. Despite two more episodes of chills and fever, and persistent stiffness of the knees, he continued to work. He had taken no medication except aspirin. When he was examined by one of the authors (H. M. C.) on March 6, 1954, he looked chronically ill. His temperature was 99°F. (orally), blood pressure normal, and heart murmurs unchanged. Despite the absence of characteristic physical findings, the history was such that subacute bacterial endocarditis was suspected and hospitalization was advised. This was refused. The patient returned home and continued to work despite the daily afternoon occurrence of fever and exhaustion. He finally consented to hospitalization for study and treatment on March 21, 1954.

On physical examination at admission the weight was 189 pounds, temperature 99.2°F. (rectal), pulse 88 per minute and respirations 18 per minute. The blood pressure was 140/50 in the right arm with the patient supine. There were no petechiae and there was no rash. The lungs were clear. The heart appeared slightly enlarged by percussion, the rhythm was regular and the aortic and pulmonic second sounds were equal in intensity. A grade 3 harsh, systolic murmur was heard, best in the aortic area, and was transmitted to both sides of the neck. At the apex, the first sound was absent; there was a grade 2 murmur which began late in diastole and extended into systole. No organs were palpable in the abdomen and there was no peripheral edema.

The hemoglobin was 15 gm. per cent and the hematocrit 47 per cent. The erythrocyte sedimentation rate (Wintrobe) was 23 mm. per hour. Total leukocytes were 8,350 per mm.^{3}, with 55 per cent polymorphonuclear forms, 40 per cent lymphocytes, 1 per cent monocytes and 4 per cent eosinophils. A second white blood count forty-eight hours after admission was 10,350. Fasting blood sugar and non-protein nitrogen were normal. Two specimens of urine were normal. Antistreptolysin O was not elevated (125 units). Venous pressure, arm-tongue circulation time and an electrocardiogram were all within normal limits. A culture of the throat grew out only normal flora. There was no growth in any of the six blood cultures taken during the first forty-eight hours in the hospital.

During the four days of this hospital stay the patient was asymptomatic except for a complaint of stiffness of the left elbow. Films of this area revealed no abnormalities. The highest temperature recorded was 100.2°F. (rectal) at 8 P.M. of the day of entry. By radiographic examination there was no abnormality of the paranasal sinuses, and there was no over-all cardiac enlargement. Films of the jaws disclosed a density near the site of the second left maxillary bicuspid, consistent in appearance with a broken root fragment. Since the patient was asymptomatic and no evidence substantiating the diagnosis of endocarditis had been obtained, he was discharged on March 25, 1954. He was advised to keep a daily record of his temperature and to report any fever, or any new clinical development. Several days after discharge the tooth fragment was removed; no pus was found at operation. Prior to and after this surgery he was given 1,000,000 units crystalline penicillin G intramuscularly.

One day after discharge from the hospital the patient noted onset of stiffness in all large joints except the ankles. This persisted for about two weeks and then disappeared. Pain and stiffness reappeared in the knees only three days before re-entry into the hospital. Two weeks prior to readmission the patient noted pain in the pads of the fourth and fifth fingers of the left hand; after one or two days the pain disappeared. During the interval between admissions the patient was unduly tired on returning from work each evening. His appetite fell off. Although there were no chills, the patient felt feverish, usually in the late afternoon, and there were episodes of copious nocturnal hidrosis. At times there was some headache associated with the fever. A sense of imbalance manifested itself by a tendency to bump into doorways. The patient was advised to return to the hospital for re-evaluation but it

was not until April 26, 1954, that he consented to do so.

Physical examination on re-entry disclosed a weight of 190 pounds, temperature of 100.6°F. (rectal), pulse of 88 and respiration of 20 per minute. The blood pressure was 134/64 in the right arm with the patient supine. One petechia was seen in the nail bed of the fourth finger of the left hand. There was no swelling or tenderness of the finger pads. The heart murmurs were definitely changed from those heard at the time of the first admission. There was a grade 3 systolic murmur at the aortic area transmitted to both sides of the neck. A grade 2, blowing diastolic murmur was heard to the right of the sternum in the second intercostal space, and also to the left of the sternum in the third and fourth intercostal spaces. There was a grade 2 systolic murmur at the apex which could be heard well into the left axilla. The spleen was not felt.

During the next two days nine blood cultures were planted and serum was obtained for serologic testing. The hemoglobin was 13 gm. per cent, the hematocrit 42 per cent and the erythrocyte sedimentation rate 42 mm. per hour. Total leukocytes were 9,350 per mm.^{3}, with 75 per cent neutrophils, 18 per cent lymphocytes, 2 per cent monocytes and 4 per cent eosinophils. The urine was normal. A chest film disclosed no significant change from the film taken at the first admission. An electrocardiogram was again normal.

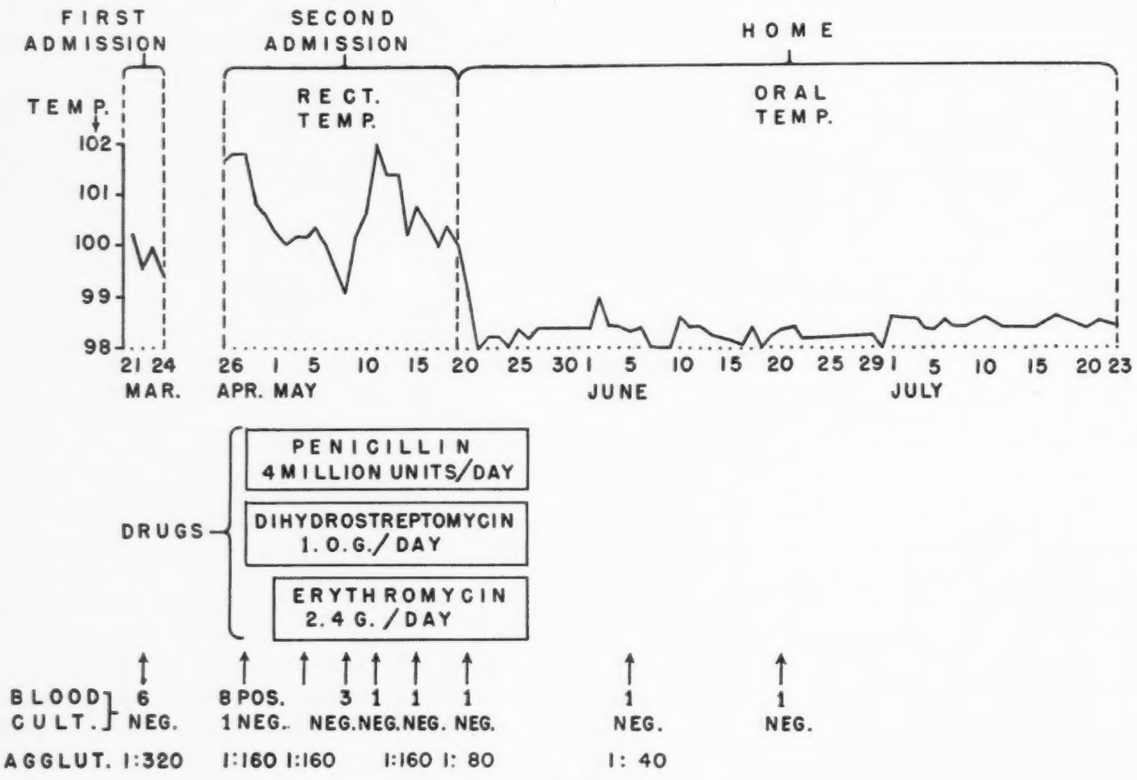


FIG. 1. Summary of clinical course.

Fever persisted and on April 28, 1954, a petechia appeared on the mid-upper lip. The spleen was palpated for the first time on this day, but was not felt again until May 11th. In the belief that the patient had subacute bacterial endocarditis, he was empirically started on a regimen of 1,000,000 units of crystalline penicillin G, intramuscularly, every six hours, and dihydrostreptomycin, 0.5 gm. intramuscularly, every twelve hours. The clinical course has been summarized in Figure 1.

On the following day brucella, typhoid and paratyphoid agglutinations were reported as being negative. Growth was noted in the earliest blood cultures and a gram-positive bacillus was reported. The initial therapeutic regimen was maintained until further identification and sensitivity studies could be completed.

New petechiae were noted on the lips on April 30th. The cardiac murmurs were un-

changed but the temperature was significantly lower. The urine was again free of cells. The results of sensitivity tests run with the bacillus isolated from the blood cultures were reported. (Table 1.) Therapy was altered on May 1st only by the addition of 0.6 gm. of erythromycin, by mouth, every six hours. The temperature curve was definitely swinging downward at this time.

Erythematous, pruritic wheals appeared on the skin of the wrists, thighs and elbows on May 4th. No new petechiae were found. Administration of antihistamine medication gave some relief from itching. On May 6th, since new wheals were still appearing, penicillin G was discontinued and crystalline penicillin O was substituted in the same dosage. The urine was clear on May 6th but on May 7th there were three to four red cells, and a rare white cell per high power field. By May 8th the wrist lesions were subsiding, but the lower leg lesions were red, confluent, 5 by 10 cm. patches, which were slightly pruritic. There were no red cells in the urine at this time and none were found subsequently.

On May 9th dull, steady, lower left chest pain was noted. Physical examination revealed no new findings. During the next two days the chest pain persisted but assumed a pleuritic character, and was accompanied by left upper quadrant abdominal pain. At this time, May 11th, the hemoglobin was 14 gm. per cent, white count 19,250 with 78 per cent neutrophils, 17 per cent lymphocytes, 4 per cent monocytes and 1 per cent eosinophils. Late evening elevation of temperature accompanied the onset of the chest pain; by May 11th the temperature remained elevated throughout the day, attaining a maximum of 102°F. Chest films were read as showing left lower lobe pulmonary infarction and definite cardiomegaly. An abdominal film disclosed one dilated loop of small bowel but there were no physical findings suggestive of mesenteric thrombosis. At this time there was a decrease in breath sounds and tactile fremitus over the left lower chest, and a tender, palpable spleen. In the legs there was no venous distention, no change in skin temperature and no abnormal consistency or tenderness in the calf muscles. The stool was guaiac-negative.

By May 14th the temperature had fallen to 100°F. Pain and signs persisted in the chest but the spleen was no longer palpable. On May 17th the chest pain was much decreased. The left diaphragm was still elevated by radiography but the density had markedly cleared. Both breath sounds and tactile fremitus were still decreased at the left base. The hemoglobin was 13 gm. per cent, white count 17,650, with 64 per cent neutrophils, 25 per cent lymphocytes, 7 per cent monocytes and 4 per cent eosinophils.

TABLE 1
SENSITIVITY OF LISTERIA MONOCYTOGENES, STRAIN ISOLATED FROM PATIENT IN THIS REPORT TO VARIOUS ANTIBACTERIAL AGENTS

Agents	Concentration	Result
Single:		
Sulfathiazole	1 mg./ml.	Resistant
Sulfadiazine	1 mg./ml.	Resistant
Sulfamerazine	1 mg./ml.	Resistant
Bacitracin	20 μ/ml.	Slightly sensitive
Chlortetracycline	10 μg./ml.	Very sensitive
Oxytetracycline	10 μg./ml.	Very sensitive
Tetracycline	10 μg./ml.	Very sensitive
Chloramphenicol	10 μg./ml.	Very sensitive
Erythromycin	1 μg./ml.	Very sensitive
Streptomycin	10 μg./ml.	Moderately sensitive
	100 μg./ml.	Very sensitive
Penicillin	1.5 μ/ml.	Resistant
	10.0 μ/ml.	Very sensitive
Combined:		
Penicillin	1.5 μ/ml.	Very sensitive
Streptomycin	10 μg./ml.	
Penicillin	1.5 μ/ml.	Resistant
Sulfisoxazole	1 mg./ml.	
Penicillin	1.5 μ/ml.	Very sensitive
Oxytetracycline	10 μg./ml.	
Penicillin	1.5 μ/ml.	Very sensitive
Chloramphenicol	10 μg./ml.	
Streptomycin	10 μg./ml.	Very sensitive
Chlortetracycline	10 μg./ml.	
Streptomycin	10 μg./ml.	Very sensitive
Oxytetracycline	10 μg./ml.	
Streptomycin	10 μg./ml.	Slightly sensitive
Chloramphenicol	10 μg./ml.	

Pain and signs had disappeared from the chest by May 19th. The temperature hovered around 100°F., an elevation thought consistent with the patient's demonstrated penicillin hypersensitivity. The patient was allowed to go home on this day, to continue one more week on all three antibiotics in the same dosage as given in the hospital. He was instructed to measure his temperature daily and keep a record of the readings. When seen at home during this final week of antibiotic therapy he was found to have remained afebrile and asymptomatic.

On June 4th, ten days after cessation of antibiotic therapy, a blood culture showed no growth. At that time, the hemoglobin was 13 gm. per cent, hematocrit 42.5 per cent, white count 12,350, with 53 per cent neutrophils, 33 per cent lymphocytes, 5 per cent monocytes, 8 per cent eosinophils and 1 per cent basophils. Two

weeks later a blood culture again showed no growth.

When examined on July 8th the patient felt quite well. His record of temperature readings disclosed no fever during the six-weeks' period following discontinuance of antibiotic therapy. There was no dyspnea on moderate exertion, and the patient was eager to go back to work. The cardiac findings remained as previously described and were the only abnormality on physical examination. An electrocardiogram was again normal. Re-examinations in the months of August, September and October failed to reveal any evidence of clinical relapse.

Bacteriologic Studies. Eight of the nine blood cultures drawn during the first forty-eight hours of the second hospital admission grew out gram-positive bacilli. Cultures taken on May 7th (No. 10, 11, 12), May 11th (No. 13), May 13th (No. 14), May 19th (No. 15), June 4th (No. 16) and June 18th (No. 17) were all sterile.

This organism grew readily on the usual laboratory media. Hemolysis occurred on blood agar, but took two to four days to appear on initial isolation. The bacillus was motile, both by hanging drop inspection and by growth in semi-solid medium. When offered various sugars, no gas was formed but acid was produced from: glucose, lactose, sucrose (late), maltose, mannitol, salicin, xylose and rhamnose. No reaction occurred with inulin, inosite, dulcite or arabinose. Citrate was not utilized, indole was not produced and H_2S was not formed. Urea was split.

Forty-eight hours after inoculation of the conjunctiva of an adult albino rabbit by swabbing gently with a twenty-four-hour broth culture, there followed a purulent conjunctivitis.[7,8] By microscopic examination, gram-positive bacilli could be seen within the leukocytes of the exudate. Culture of this pus grew out only gram-positive bacilli.

An adult albino mouse was given, by intraperitoneal injection, 0.5 ml. of a twenty-four-hour broth culture. This mouse died after ninety-six hours. At necropsy the liver, spleen and mesentery were studded with small, pin-head sized, white nodules. Cultures of these nodules, peritoneal exudate, heart blood, all grew out gram-positive bacilli in pure culture.

This combination of morphology, cultural characteristics, biochemical reactions and pathogenicity is sufficiently unique to identify this organism as Listeria monocytogenes.

Agglutination Studies. Using live, twenty-four-hour cultures of the Listeria isolated from the patient (grown in trypticase-soy medium at 37°C.), the patient's serum was tested for agglutinins. Serum was diluted with sterile saline to which had been added crystalline penicillin G (final concentration 10 units per ml.) and streptomycin (final concentration 25 μg. per ml.). To 0.5 ml. amounts of each serum dilution, in 10 by 75 mm. tubes, was added 0.5 ml. of the culture. The tubes were capped with parafilm, mixed by repeated inversion, and incubated at 37°C. for two hours. After twenty-four hours in the refrigerator they were read. Firm edges to the agglutinated button, together with a clear supernatant, were taken as evidence of complete agglutination (designated C in Table II). Slight turbidity, as compared with the saline control, a diffuse edge to the precipitate, and coherent masses spinning up on tapping the tube, were taken as signifying incomplete agglutination (designated I in Table II). Lesser degrees of agglutination were considered too subjective in reading to be worthy of reporting (designated 0 in Table II). Agglutinations were attempted using formalinized bacteria. A twenty-four-hour broth culture was treated with 1/50 volume of 37 per cent formalin by incubation at 37°C. for twenty-four hours; the bacteria were washed twice with normal saline, re-suspended in normal saline for use. With this antigen, agglutination was observed in all tubes, including the saline control.

TABLE II
AGGLUTINATION OF LISTERIA ISOLATED FROM THE PATIENT BY THE PATIENT'S OWN SERUM (SEE TEXT FOR METHODOLOGY)

Date	Final Dilution								
	1:10	1:20	1:40	1:80	1:160	1:320	1:640	1:1280	Saline
March 22, 1954	C	C	C	C	C	C	I	0	0
April 27, 1954	C	C	C	C	C	I	0	0	0
May 4, 1954	C	C	C	C	C	I	0	0	0
May 13, 1954	C	C	C	C	C	I	0	0	0
May 19, 1954	C	C	C	C	I	0	0	0	0
June 4, 1954	C	C	C	I	0	0	0	0	0
Control*	C	I	0	0	0	0	0	0	0
Normal†	0	0	0	0	0	0	0	0	0

C = complete agglutination; I = definite, but incomplete agglutination; 0 = no definite agglutination.

* Control serum obtained from a patient in first week of therapy for Strep. viridans subacute bacterial endocarditis.

† Normal serum obtained from one of the authors (P. H.).

Control serum was obtained from a patient ill with subacute bacterial endocarditis due to Streptococcus viridans; this patient was in her first week of therapy. Normal serum was obtained from one of the authors (P. D. H.). The agglutination results are tabulated in Table II; serum from the first admission (March 22nd) was also tested for agglutinins.

COMMENTS

One can only speculate as to when this patient's illness began. From the agglutination and historical data he must have been ill for some time before his admission on March 21, 1954. He was known to have had occasional episodes of fever for at least three weeks prior to this admission. He had experienced arthralgia and asthenia four months before this admission and it is possible that his disease began at this time. Since subacute bacterial endocarditis frequently follows dental surgery and usually has an insidious onset, it is not impossible that the disease began as far back as the dental surgery of June and July, 1953. In favor of a shorter duration of illness was the finding at the initial admission of a normal hemogram, and the development during the interval between admissions of the anemia characteristic of subacute bacterial endocarditis. As far as could be ascertained, the patient had no contact with animals that might have been infected with Listeria.

The source of the embolus causing infarction of the left lower lobe of the lung could not be definitely fixed. There was no clinical evidence of leg vein thrombophlebitis. While there were no definite signs of tricuspid or pulmonary valve disease, involvement of these valves might have been masked by murmurs arising from the already diseased aortic and mitral valves.

Urticaria, due to allergy to penicillin G, was the only untoward effect engendered by the antibiotic therapy given this patient. By substituting penicillin O for the offending penicillin G, and giving antihistamine medication, it was possible to continue to give large doses of penicillin with minimal discomfort to the patient.

Of most interest in this case is the finding in the patient's serum of a significant level of agglutinins for the Listeria causing his illness. It should be emphasized that except for two reports, to be discussed, studies on immunity in human Listeria infections have failed to reveal significant antibody levels.

Janeway and Dammin[9] pointed out the Listeria agglutinating power of horse serum. In serum from a patient acutely ill with Listeria meningitis, Carey[10] reported Listeria agglutination in a dilution of 1:640. Because this patient had received anti-meningococcus horse serum, and since there were no agglutinins in serum obtained two weeks after recovery, the initial high titer probably represented passively obtained horse serum agglutinins.

Kapsenberg[11] reported a titer of 1:800 in a patient ill with Listeria meningitis. No information was given as to time during illness when this serum was obtained, or what preceding and succeeding titers were. The patient survived and it was mentioned that sulfapyridine was used in treatment; no statement as to whether or not horse serum had been given was included. Further, there was no description of the agglutination method and no mention was made of control sera.

Beute et al.[12] described listerosis in a sixty-nine year old woman. This illness apparently began as a severe conjunctivitis, with signs and symptoms of meningitis developing about a week later. Listeria was isolated from the cerebrospinal fluid. Sera from the patient were tested for agglutinins active against the Listeria isolated, with these results:

1 week after onset of conjunctivitis (4 days after meningitis)	negative
3 weeks after onset of conjunctivitis (17 days after meningitis)	1:1600
5 weeks after onset of conjunctivitis (32 days after meningitis)	1:800

Penicillin and sulfonamide therapy secured recovery; there was no mention of horse serum administration. The agglutination method was not described nor was use of control sera.

Bennett et al.[13] in reporting a case of Listeria meningitis sought serum agglutinins against the infecting Listeria. No agglutinins were found in sera obtained from the twelfth to the thirty-fifth hospital day. Both live and formalinized bacteria were used.

Line and Cherry[14] described two cases of Listeria meningitis. Using formalinized bacteria, complete agglutination was not obtained beyond a final dilution of 1:50; a trace was reported at a final dilution of 1:200.

Finegold et al.[15] looked for agglutinins in one of their two cases of Listeria meningitis. They obtained only partial agglutination at a final

dilution of 1:40 with acute serum and 1:80 with convalescent serum. Formalinized bacteria were used in their studies.

From these data it seems most likely that significant agglutination titers are not associated with Listeria meningitis. Infectious mononucleosis, according to Webb's case,[16] also does not make for high agglutinin titers. He reported a classic case of infectious mononucleosis (heterophile titer of 1:2048); Listeria was isolated from the blood. This patient's serum gave only a trace agglutination at a 1:25 dilution on the thirty-seventh day after onset of the illness. One year later the same titer was obtained.

Janeway and Dammin[9] found no significant quantity of agglutinin for Listeria in the sera of thirteen patients ill with indisputable infectious mononucleosis.

The finding, then, of subacute bacterial endocarditis due to Listeria, while in itself unique, presents one of the few instances of Listeria infection in which significant antibody production has been demonstrated. Just as the non-invasive character of Listeria might lead one to predict it would be found to cause subacute bacterial endocarditis, so might one also predict that in such an infection significant levels of antibody would obtain, as the allergic aspects of subacute bacterial endocarditis pathogenesis demand.[17–19]

SUMMARY

1. A case of subacute bacterial endocarditis due to Listeria monocytogenes is described. A review of the writings on both human Listeria infections and bacterial endocarditis has disclosed no previously reported case of subacute bacterial endocarditis due to this organism.

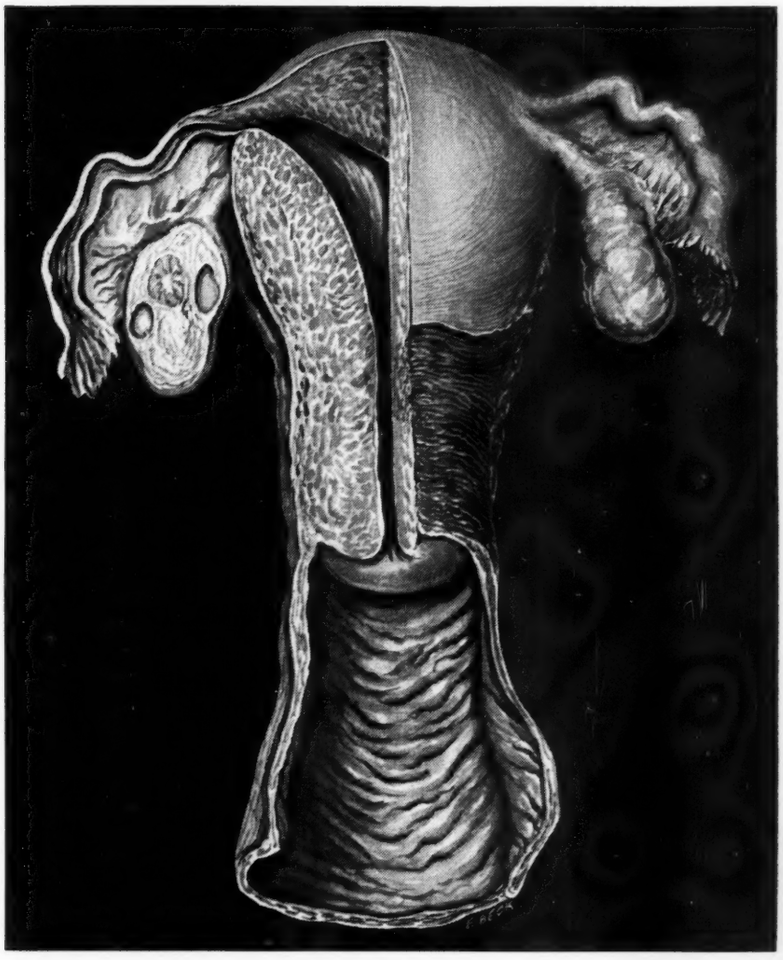
2. Significant levels of agglutinins active against the Listeria causing the patient's illness were demonstrated in his serum. The agglutinin titer fell from 1:320 in the untreated state to 1:40 after cure. In more common forms of human Listeria infection significant agglutinin titers have rarely been reported.

3. Antibacterial therapy consisted of concomitant administration of crystalline penicillin, dihydrostreptomycin and erythromycin. Five months after cessation of therapy, there was no indication of relapse.

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*Sturnick, M. I., and Gargill, S. L.: New England J. Med. *247*:829 (Nov. 27) 1952.

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—Rohn, R. J.; Bond, W. H., and Klotz, L. J.: J. Indiana State Med. Assn. *46*:1253 (Dec.) 1953.

"Cobalt appears to be of value in the prevention of the early anemia of premature infants, and if iron is administered simultaneously the risk of an iron deficiency anemia developing from the fourth month onwards is considerably reduced."

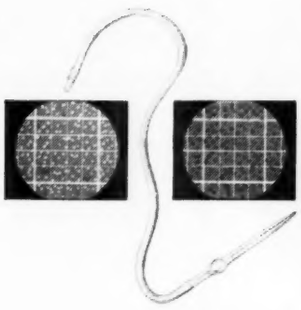
—Coles, B. L., and James, U.: Archives of Disease in Childhood, *29*:85 (April) 1954.

As compared with controls, 16 premature infants receiving Roncovite Drops showed "significantly greater values in the mean hemoglobin and hematocrit levels..."

—Quilligan, J. J., Jr.: Texas St. J. Med. *50*:294 (May) 1954.

IN PREGNANCY—"...57 of the 58 patients (98.2 per cent) maintained or improved their hemoglobin [with Roncovite]."

—Holly, R. G.: Obstet. & Gynecol., *5*:562 (April) 1955.



IN CHRONIC LOW-GRADE INFECTIONS—"Cobalt appears to be a valuable drug in the treatment of anemias secondary to chronic diseases."

—Weinsaft, P. P., and Bernstein, L. H. T.: Amer. J. Med. Sc., Vol. 229, (Sept.) 1955.

"In all patients (chronic suppurative infection) a reticulocytosis was observed within 6 days. This was followed by increases in red-cell counts, in hemoglobin values, in blood volume and in total circulating hemoglobin."

—Robinson, J. C., et al.: New England J. M. *240*:749 (May) 1949.

Safe Medication

IN INFANCY—"There were no toxic effects in any case."

—Coles, B. L.: Archives of Disease in Childhood, *30*:150 (April) 1955.

"None of them [infants] showed harmful effects despite the large doses."

—Quilligan, J. J., Jr.: Texas St. J. Med. *50*:294 (May) 1954.

IN PREGNANCY—"No toxic manifestations associated with its use have been observed."

—Holly, R. G.: Obstet. & Gynecol. *5*:562 (April) 1955.

IN CHRONIC LOW-GRADE INFECTIONS—"With 60 mg. (cobalt chloride) a day by mouth after meals neither ourselves nor our patients experienced untoward symptoms."

—Robinson, J. C., et al.: New England J. M. *240*:749 (May) 1949.

"In our hands, cobalt appeared to be a useful and valuable drug, well tolerated and devoid of undue toxicity."

—Weinsaft, P. P., and Bernstein, L. H. T.: Amer. J. Med. Sc., Vol. 229, (Sept.) 1955.

AND . . . Thorough investigation has again verified the safety and lack of toxicity of Roncovite. Please refer to the four articles in the August 13, 1955 issue of the J.A.M.A. (Volume 158, No. 15) which fully document this convincing evidence.

RONCOVITE®

The original, clinically proved, pure *cobalt-iron product.*

LLOYD BROTHERS, INC.

Cincinnati 3, Ohio

SUPPLIED:

RONCOVITE TABLETS

Each enteric coated, red tablet contains:

Cobalt chloride	15 mg.
Ferrous sulfate exsiccated	0.2 Gm

Bottles of 100

RONCOVITE-OB

Each enteric coated red capsule-shaped tablet contains:

Cobalt chloride	15 mg.
Ferrous sulfate exsiccated	0.2 Gm
Calcium lactate	0.9 Gm.
Vitamin D	250 units

Bottles of 100

RONCOVITE DROPS

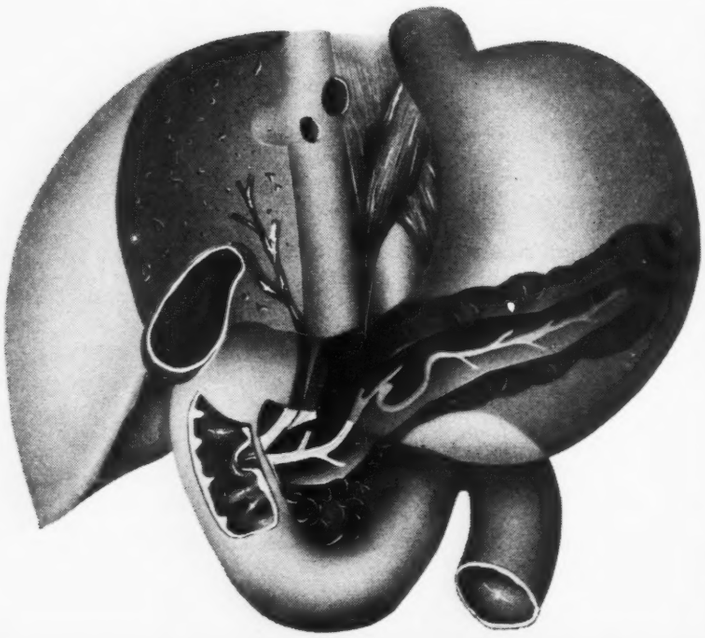
Each 0.6 cc. (10 drops) provides:

Cobalt chloride (Cobalt 9.9 mg.)	40 mg.
Ferrous sulfate	75 mg.

Bottles of 15 cc. with calibrated dropper

DOSAGE:

One tablet after each meal and at bedtime. Children 1 year or over, 0.6 cc. (10 drops); infants less than 1 year, 0.3 cc. (5 drops) once daily diluted with water, milk, fruit or vegetable juice.



constipation
and
related
functional
G. I. distress

markedly relieved in
8 out of 10 patients*
by inexpensive, physiologic
stimulant

DECHOLIN® with Belladonna

improved liver function* PLUS *reliable spasmolysis

Steps up flow of dilute bile by *hydro*choleresis • physiologic elimination without catharsis • relieves spasm • no cramping • no evidence of tolerance • helps establish normal bowel habits

One or, if necessary, two *Decholin*/Belladonna Tablets t.i.d. gives your patients more effective relief of constipation and related G.I. complaints: flatulence, bloating, belching, nausea and indigestion.

Each tablet contains *Decholin* (dehydrocholic acid, *Ames*) 3¾ gr., and extract of belladonna ⅙ gr. (equivalent to tincture of belladonna, 7 minims). Bottles of 100 and 500.

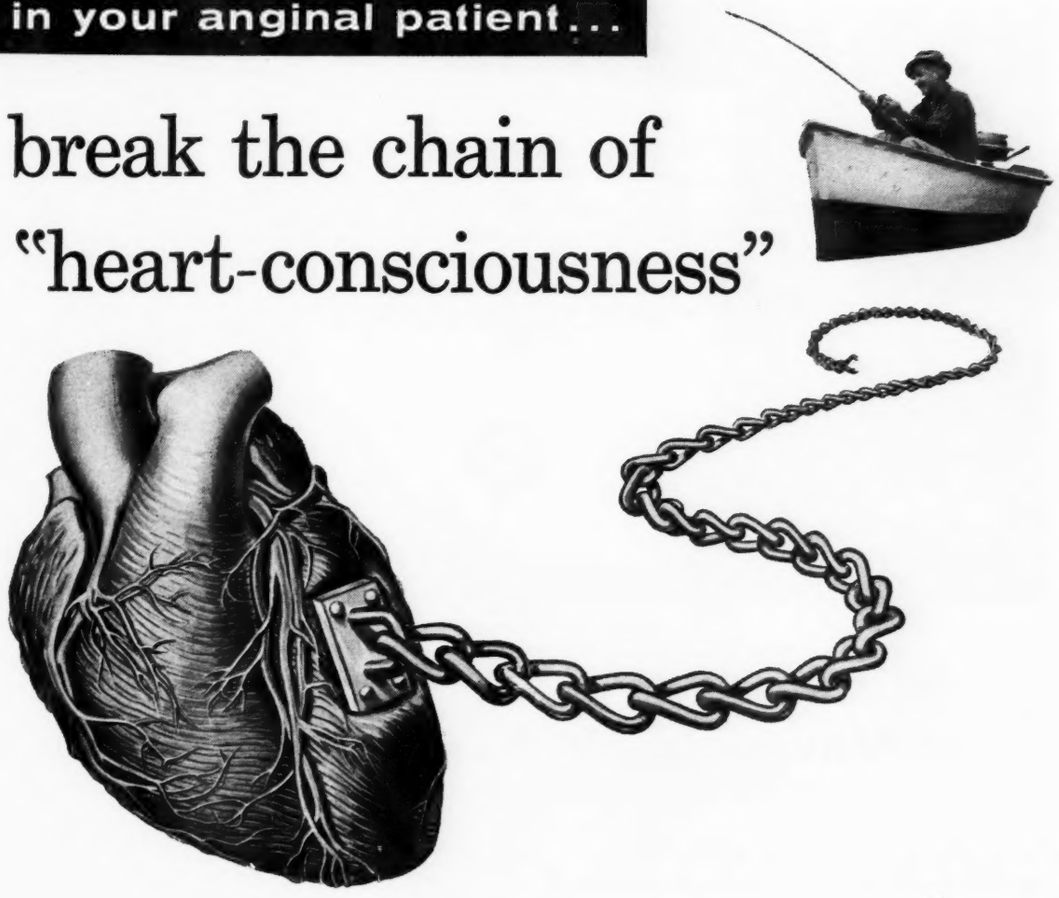
*King, J. C.: Am. J. Digest. Dis. *22*:102, April, 1955.

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COMPANY, INC • ELKHART, INDIANA • Ames Company of Canada, Ltd., Toronto

03555

in your anginal patient...

break the chain of "heart-consciousness"



Your anginal patient can be freed from his "heart-consciousness" for a wider range of activities by the daily administration of Nitralox which aids in protecting him against the bodily and emotional factors which so often precipitate anginal seizures. Nitralox generally lessens the frequency and severity of attacks, will often lower nitroglycerin requirements, increase exercise tolerance and improve the electrocardiogram.

In anginal patients with hypertension and tachycardia, Nitralox has the added advantage of reducing the blood pressure and slowing the pulse. It has no such effects in normotensives with normal heart rates.

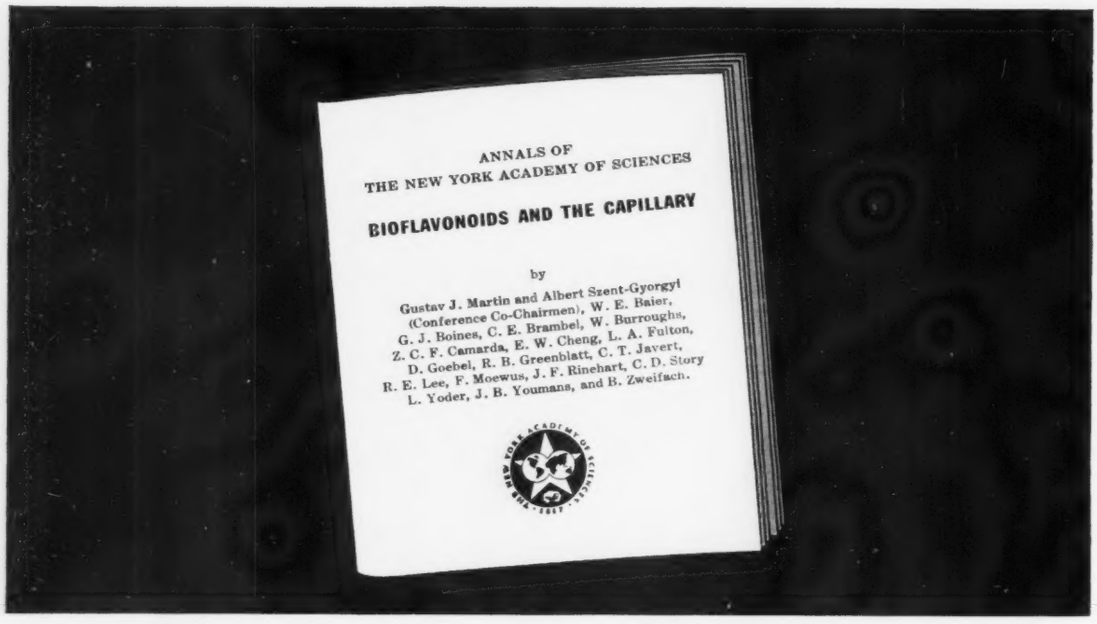
Nitralox combines a coronary vasodilator with prolonged action (10 mg. pentaerythritol tetranitrate – PETN) with a nonbarbiturate tranquillizing and bradycrotic agent (1 mg. purified mixed Rauwolfia alkaloids – the alseroxylon fraction) and is intended for long-term prophylactic therapy. While some patients experience beneficial effects within 24-48 hours, it takes about two weeks before Nitralox produces its full effect from the recommended dosage of 1-2 tablets q.i.d. before meals, and at bedtime.

NITRALOX

for long-range management of anginal attacks

Nitralox is a DORSEY preparation

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Latest report on the values of the bioflavonoids in health and disease

This free monograph of the recent Bioflavonoid Conference should be read by every doctor.

A recent symposium, bringing together current thoughts and findings on the chemistry, biochemistry and biological actions of the bioflavonoids, has supplied further evidence of the important role played by the flavonoid materials in both health and disease.

Focal point of the discussions was the value of the flavonoids to the capillary system... how they aid in the maintenance of normal capillary integrity and aid in the treatment of impaired capillary function.

Other papers and discussions covered the application of the bioflavonoids to the management of rheumatic fever, habitual abortion, poliomyelitis and their role in anticoagulant therapy. Discussions emphasized the importance of the relationship of the bioflavonoids with vitamin C.

Complete information on the symposium proceedings, monograph of the talks and notes on the discussions are available on request. Write Sunkist, Box 2706, Terminal Annex, Los Angeles 54, California.

The flavonoids are widely distributed in nature but are especially abundant in fresh oranges and lemons.

Fresh lemon juice has been established as an important source. In oranges the bioflavonoids are found mainly in the cell walls and fibrous tissues of the fruit rather than the juice. The whole peeled orange contains 10 times as much bioflavonoid as the finely strained juice alone.

The bioflavonoids are another reason for the increasing interest in citrus in its natural form... fresh.

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Sunkist citrus is recognized as the finest in any market... anywhere.

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the metabolic

approach

to the successful

treatment of

PSORIASIS

Since an etiological factor in psoriasis may be a metabolic defect, causally related to inadequate intestinal digestion, replacement therapy with Entozyme is entirely rational. In a recent study, 19 out of 24 patients recalcitrant to all previous treatment showed "good response...within four weeks to three months... complete clearing in four cases."*

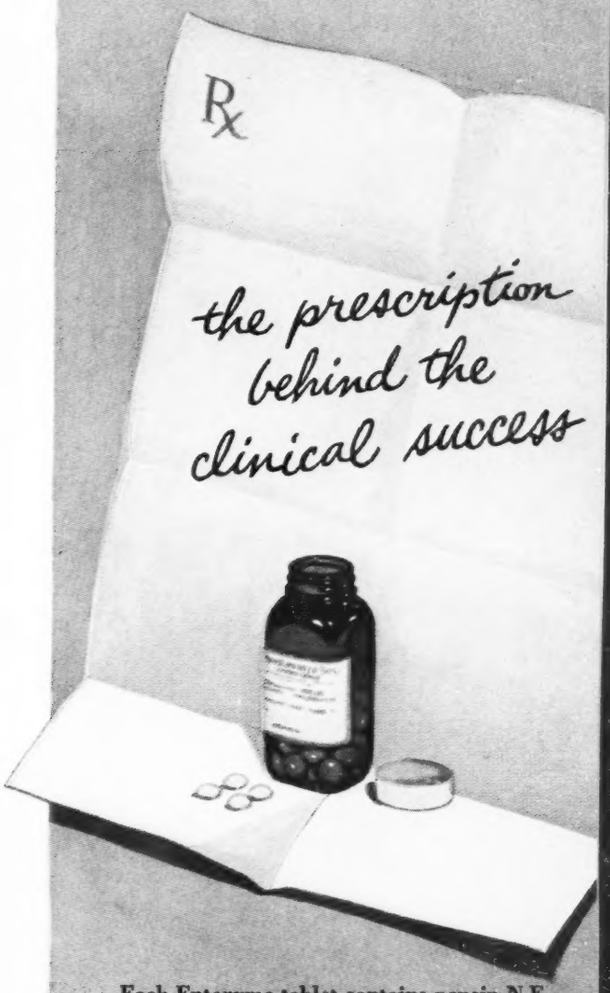
*Ingels, A. H.: California Med. 79:437, 1953.

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Digestive Enzyme Replacement

A. H. Robins Co., Inc., Richmond 20, Va.

Ethical Pharmaceuticals of Merit since 1878

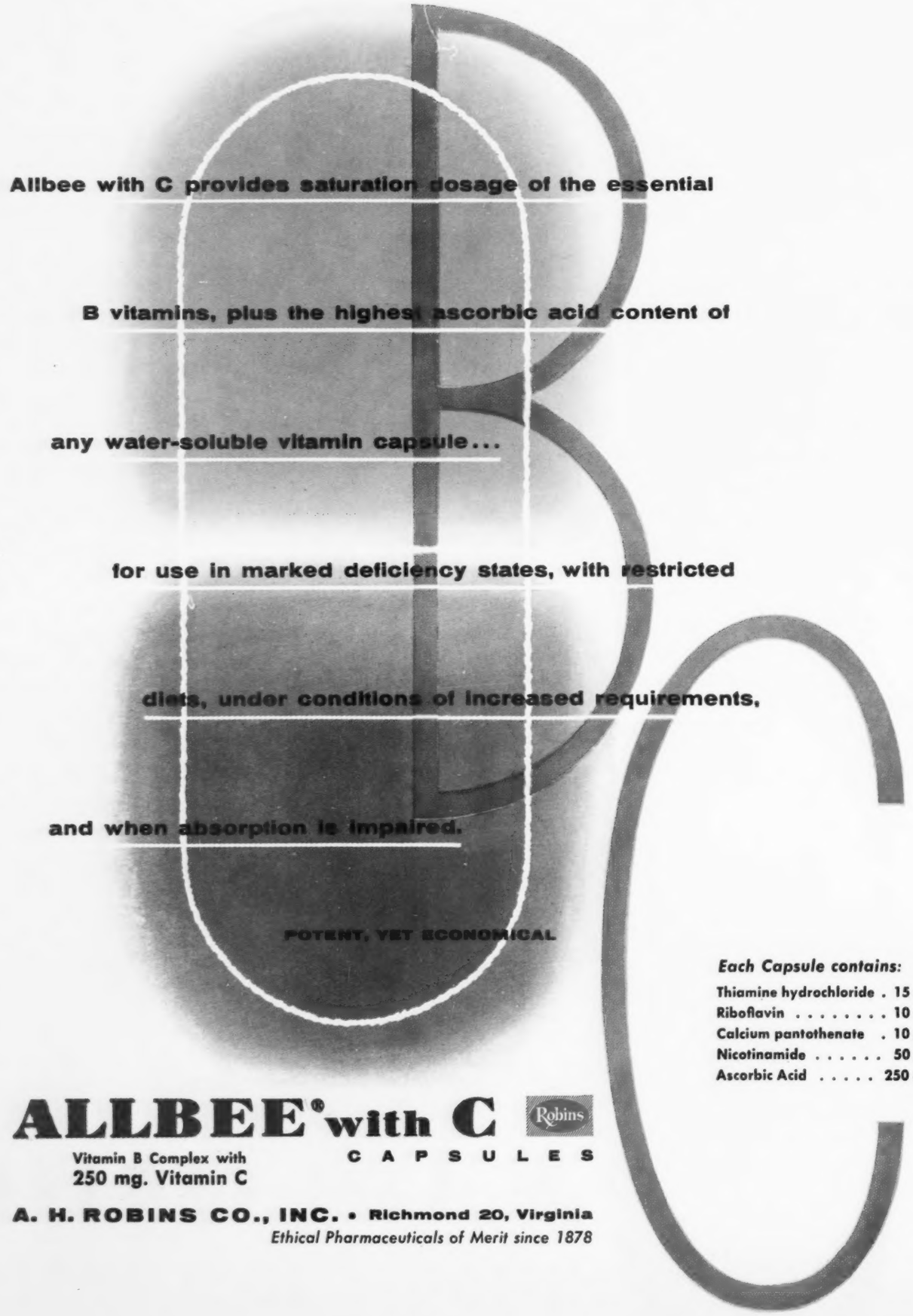


Each Entozyme tablet contains pepsin N.F. 250 mg., pancreatin U.S.P. 300 mg., bile salts 150 mg. Completely non-toxic.



In addition to its efficacy in the treatment of psoriasis, Entozyme is indicated in a wide range of chronic nutritional disturbances associated with aberrations in protein metabolism, as in senescence, fatty liver syndrome, etc. It is also helpful in many acute digestive disorders.

FOR SATURATION DOSAGE OF WATER-SOLUBLE VITAMINS



Allbee with C provides saturation dosage of the essential B vitamins, plus the highest ascorbic acid content of any water-soluble vitamin capsule...

for use in marked deficiency states, with restricted diets, under conditions of increased requirements, and when absorption is impaired.

POTENT, YET ECONOMICAL

Each Capsule contains:

Thiamine hydrochloride	15 mg.
Riboflavin	10 mg.
Calcium pantothenate	10 mg.
Nicotinamide	50 mg.
Ascorbic Acid	250 mg.

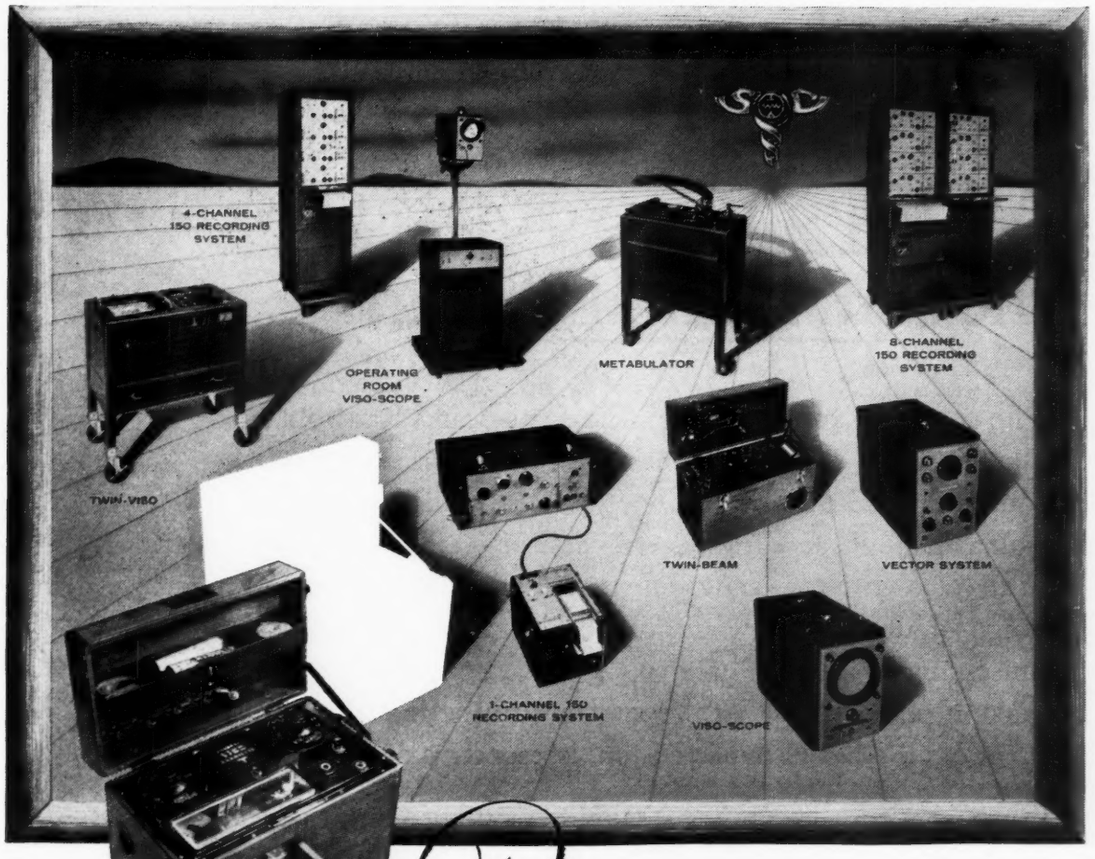
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Vitamin B Complex with
250 mg. Vitamin C

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Background

is part of every picture

IN weighing the merits of an important piece of equipment, such as an electrocardiograph, it is often helpful to know something about the maker — his qualifications, his experience, and the other acceptable instruments he makes. In short, you might like to know what sort of *background* the considered electrocardiograph has.

In the case of the Viso-Cardiette, such a background can be represented by the instruments chosen to accompany it in the Sanborn "family portrait" above. Although not possible to show them all here, Sanborn instruments of precision cover the complete range of cardiac recording for diagnosis and research, and also provide the basis for the measurement and recording of most of the other types of physiological phenomena.

Collectively, they represent the tangible application of the Sanborn experiences and skills that were gained over the past third of a century Unquestionably, such a background *does* make the Viso picture complete

Write for completely descriptive literature, or contact your local Sanborn Office for information or a demonstration.



BEFORE you buy a Viso-Cardiette, you have the opportunity to examine it thoroughly AT YOUR LEISURE and to test in your own practice for 15 DAYS WITH NO OBLIGATION WHATSOEVER

consensus of research is . . .

All hypertensives should receive the same initial therapy

The consensus of research clinicians advocates Rauwolfia alkaloids – such as Rautensin, a standardized extract containing *all* the hypotensive and tranquillizing Rauwolfia alkaloids, free from inert material – as the *first step* in all hypotensive therapy. The lack of toxicity over a wide range of dosage, the tranquillizing, headache-relieving, pulse-slowing and gradual hypotensive action of Rautensin make it one of the safest preparations in the initial treatment of all types of hypertension, irrespective of severity.



Then, too, your nervous, stress-ridden patients with *early labile hypertension* respond especially well to Rautensin. In the more stubborn cases requiring combination therapy Rautensin, used as a platform on which to build an effective regimen, usually permits reducing the dosage of other hypotensive agents. Result: Less side effects.



Each Rautensin tablet contains 2 mg. of purified Rauwolfia alkaloids (alseroxylon fraction).



Dosage: For the first 20 to 30 days 2 tablets (4 mg.) once daily before retiring; thereafter 1 tablet (2 mg.) daily usually suffices.

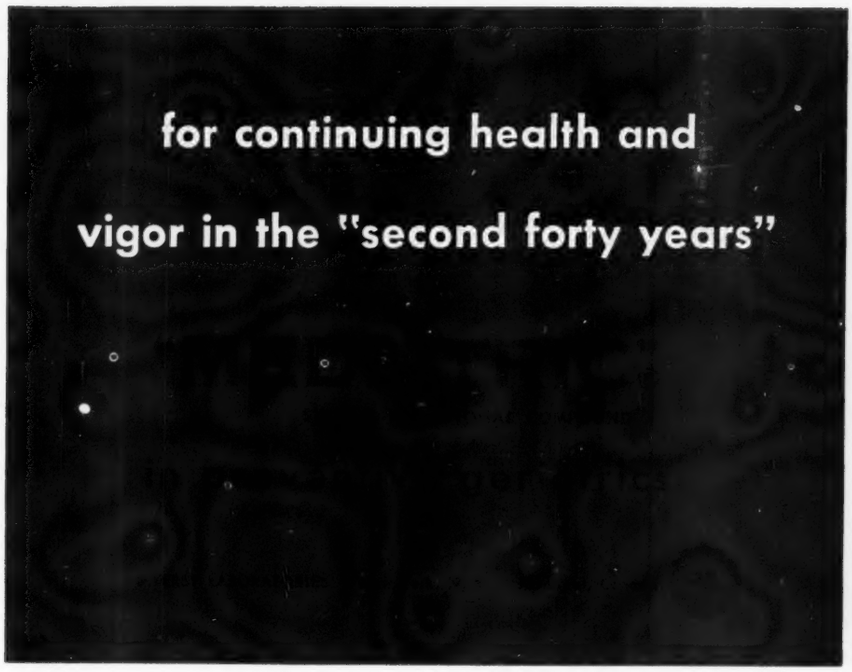


RAUTENSIN®

for basic therapy in all hypertensives

Rautensin is a DORSEY preparation

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Lederle

FOLBESYN*

Vitamins *Lederle*

A well-balanced, high-potency vitamin formula containing B-Complex and C

FOLBESYN provides B-Complex factors (including folic acid and B_{12}) and ascorbic acid in a well balanced formula. It does not contain excessive amounts of any one factor.

FOLBESYN Parenteral may be administered intramuscularly, or it may be added to various hospital intravenous solutions. It is useful for preoperative and postoperative treatment and during convalescence.

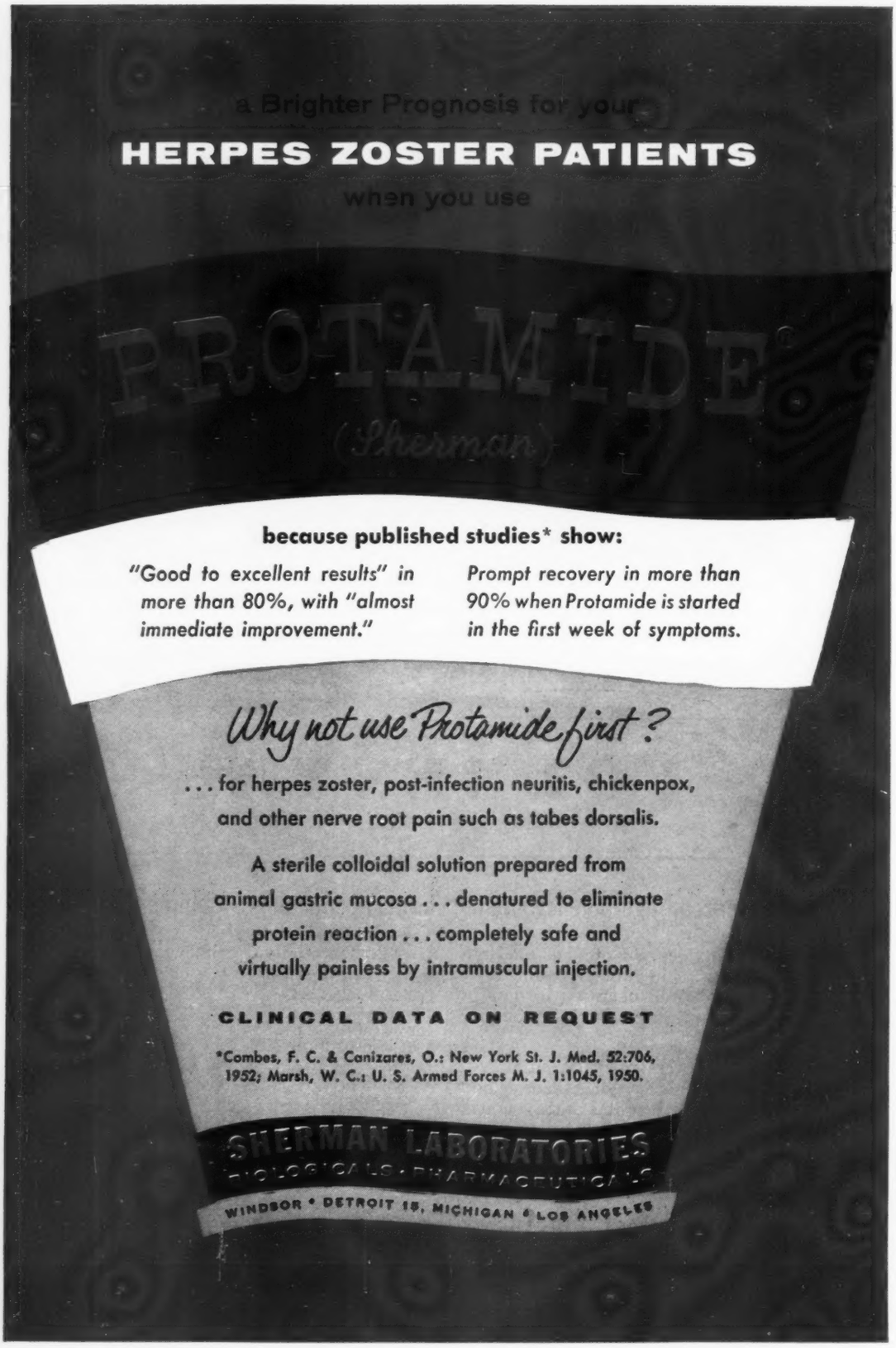
Dosage: 2 cc. daily. Each 2 cc. provides:

Thiamine HCl (B_1)	10 mg.
Sodium Pantothenate	10 mg.
Niacinamide	50 mg.
Riboflavin (B_2)	10 mg.
Pyridoxine HCl (B_6)	5 mg.
Ascorbic Acid (C)	300 mg.
Vitamin B_{12}	15 micrograms
Folic Acid	3 mg.

FOLBESYN is also available in tablet form, ideal for supplementing the parenteral dose.

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a Brighter Prognosis for your
HERPES ZOSTER PATIENTS
when you use
PROTAMIDE®
(Sherman)
because published studies* show:
"Good to excellent results" in more than 80%, with "almost immediate improvement."
Prompt recovery in more than 90% when Protamide is started in the first week of symptoms.
Why not use Protamide first?
. . . for herpes zoster, post-infection neuritis, chickenpox, and other nerve root pain such as tabes dorsalis.
A sterile colloidal solution prepared from animal gastric mucosa . . . denatured to eliminate protein reaction . . . completely safe and virtually painless by intramuscular injection.
CLINICAL DATA ON REQUEST
*Combes, F. C. & Canizares, O.: New York St. J. Med. 52:706, 1952; Marsh, W. C.: U. S. Armed Forces M. J. 1:1045, 1950.
SHERMAN LABORATORIES
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LIVITAMIN® with IRON
each fluidounce contains:

Iron peptonized ..... 420 mg.
(Equiv. in elemental iron to 70 mg.)
Manganese citrate, soluble ..... 158 mg.
Thiamine hydrochloride ..... 10 mg.
Riboflavin ..... 10 mg.
Vitamin B_{12} (crystalline) ..... 20 mcg.
Niacinamide ..... 50 mg.
Pyridoxine hydrochloride ..... 1 mg.
Pantothenic acid ..... 5 mg.
Liver fraction 1 ..... 2 Gm.
Rice bran extract ..... 1 Gm.
Inositol ..... 30 mg.
Choline ..... 60 mg.

. . . the reconstructive iron tonic of wide application . . .

LIVITAMIN®

WITH IRON

In debilitation, syndrome therapy instead of symptom treatment is required. Livitamin (Massengill) provides comprehensive therapy and adequate nutritional support. The appetite improves, as does the blood picture . . . improved anabolism and better digestion produce a significant syndrome reversal.

LIVITAMIN® CAPSULES with INTRINSIC FACTOR
each capsule contains:

Desiccated liver ..... 450 mg.
Ferrous sulfate ..... 130 mg.
(Equiv. to 25 mg. of elemental iron)
Thiamine hydrochloride ..... 3 mg.
Riboflavin ..... 3 mg.
Niacinamide ..... 10 mg.
Vitamin B_{12} ..... 5 mcg.
Pyridoxine hydrochloride ..... 0.5 mg.
Calcium pantothenate ..... 2 mg.
Folic acid ..... 1 mg.
Intrinsic factor USP ..... 1/6 Unit

. . . in pernicious anemia and geriatrics . . .

LIVITAMIN®

CAPSULES WITH INTRINSIC FACTOR

Intrinsic factor is essential to provide full utilization of antianemic and nutritional factors in P. A. and many Geriatric patients. Livitamin Capsules with Intrinsic Factor (Massengill) contain intrinsic factor, U.S.P., iron and the B-complex vitamins. This integrated medication provides an optimal response in these difficult patients.

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BRISTOL, TENNESSEE

Serpasil®

(reserpine CIBA)

Elixir

Sedation without hypnosis

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Bromural

For Daytime Tranquillity
non-barbiturate sedative

- Quick acting
- Rapidly eliminated
- Free from side effects

Dose: 1 BROMURAL tablet several times a day.

Try 1 Bromural tablet with an aspirin for quicker relief of neuralgic pain and headache, discomfort and the aches of simple colds — better than aspirin alone.

Each BROMURAL tablet bears the mark ⊕ of the originator.

Bromural, brand of Bromisovalum, a product of E. Bilhuber, Inc.

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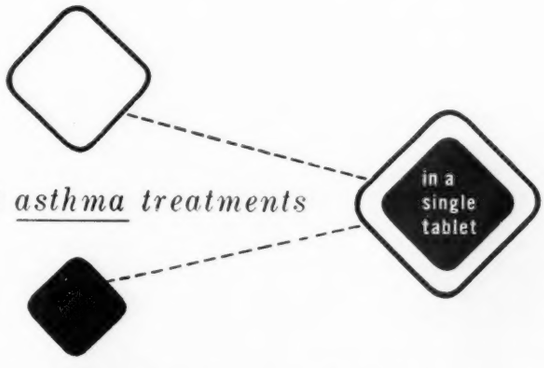
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Nonsoporific tranquilizer

Especially indicated for Old People and Children

Highly compatible vehicle

New SERPASIL ELIXIR is compatible with Pyribenzamine® Elixir, dextro-amphetamine sulfate elixir, Antrenyl® Syrup, codeine phosphate, ephedrine sulfate, sodium salicylate and many other medications. Serpasil Elixir has a clear light-green color and a pleasant lemon-lime flavor. Each 4-ml. teaspoonful contains 0.2 mg. of Serpasil.



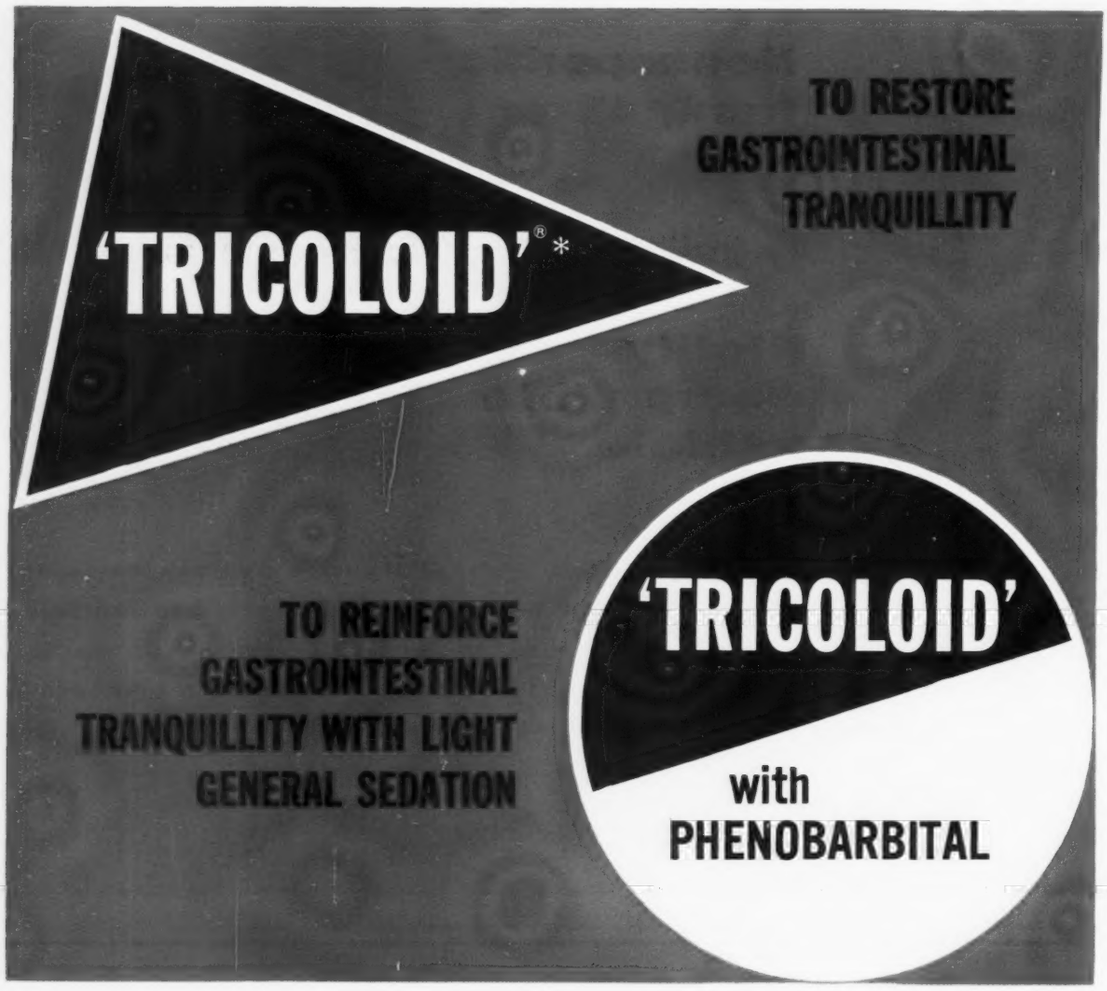
the 2 *favored asthma treatments*

First, hold tablet under the tongue 5 minutes for sublingual absorption of quick-acting aludrine (Isopropyl arterenol). Then swallow for 4-hour, follow-through protection from theophylline-ephedrine-phenobarbital in the tablet core.

There's an excellent chance your asthma patients will prefer fast acting, long-lasting convenient NEPHENALIN tablets. DOSE: One tablet as needed (up to 5 tablets a day). Bottles of 20 and 100. THOS. LEEMING & CO., INC., New York 17, N. Y.

Nephenalin® (*for adults*)

Nephenalin® PEDIATRIC



'TRICOLOID' or **'TRICOLOID' with Phenobarbital** is indicated, according to the degree of emotional tension which accompanies the symptoms, for the medical management of:

"lower bowel syndrome,"
nervous indigestion,
functional gastroenteritis,
peptic ulcer

* **'TRICOLOID'** *brand Tricyclamol 50 mg. Sugar-coated tablets*
'TRICOLOID' *brand Tricyclamol 50 mg. with Phenobarbital 16 mg. (gr. ¼) Sugar-coated tablets*

Both products in bottles of 100 and 1,000

BURROUGHS WELLCOME & CO. (U.S.A.) INC., *Tuckahoe, New York*

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in Antibiotic Therapy— **POLYCYCLINE**
a tetracycline produced by a unique process of direct fermentation

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FOR SUPERIOR PERFORMANCE IN ANTIBIOTIC THERAPY

—effective, safer, more sustained action with this newest broad-spectrum antibiotic

Polycycline—available in many dosage forms—affords significant clinical advantages in broad-spectrum antibiotic therapy:

Effective in broad range

—against Gram-positive and Gram-negative organisms, certain rickettsiae and large viruses.

Greater tolerance

—markedly lower incidence and severity of adverse side effects.

Greater solubility

—than chlortetracycline, yielding quicker absorption and increased diffusion in body fluids and tissues.

Greater stability

—in solution than chlortetracycline or oxytetracycline, assuring higher, more sustained blood levels.

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Polycycline is a tetracycline produced by the unique Bristol process of direct fermentation. Its basic structural formula is free of a chlorine atom (present in chlortetracycline), and of an hydroxyl group (present in oxytetracycline).

When you think of Tetracycline, think of

Your pharmacist has all dosage forms of Polycycline available for your prescription:



POLYCYCLINE SUSPENSION WITH TRIPLE SULFONAMIDES

Coconut oil suspension of tetracycline with three sulfonamides. In concentration of 125 mg. tetracycline HCl with 167 mg. each of sulfadiazine, sulfamerazine and sulfamethazine per 5 cc.; in bottles of 2 fl. oz.



POLYCYCLINE AQUEOUS '250' or AQUEOUS '125'

An aqueous suspension ready to use without reconstitution. Stable for 18 months without refrigeration. Highly palatable, cherry flavor. As calcium tetracycline equivalent to 250 mg. (or 125 mg.) tetracycline HCl per 5 cc.; in bottles of 1 fl. oz.



POLYCYCLINE SUSPENSION '250'

A really palatable oil suspension, requiring no dilution or reconstitution. Needs no refrigeration—stable for 18 months. In concentration of 250 mg. tetracycline HCl per 5 cc.; in bottles of 1 fl. oz.

For accurate dosage in small amounts. In concentration of 100 mg. tetracycline HCl per cc.; in bottles of 10 cc. with dropper calibrated for administration of 25 mg. or 50 mg.

POLYCYCLINE PEDIATRIC DROPS



POLYCYCLINE AQUEOUS PEDIATRIC DROPS

As calcium tetracycline equivalent to 100 mg. tetracycline HCl per cc.; in bottles of 10 cc. with dropper calibrated at 25 mg. and 50 mg.

For deep intramuscular injection. In single-dose vials of 100 mg. tetracycline HCl per vial.

POLYCYCLINE INTRAMUSCULAR



Handy form for oral use, in two potencies of tetracycline HCl. In capsules of 100 mg.; in bottles of 25 and 100. In capsules of 250 mg.; in bottles of 16 and 100.

POLYCYCLINE CAPSULES



POLYCYCLINE OINTMENT WITH 2% XYLOCAINE*

—30 mg. tetracycline HCl with 20 mg. Lidocaine (as the base), per gram.

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POLYCYCLINE®

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for a sound sleep tonight, a calm day tomorrow . . .

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TRADEMARK

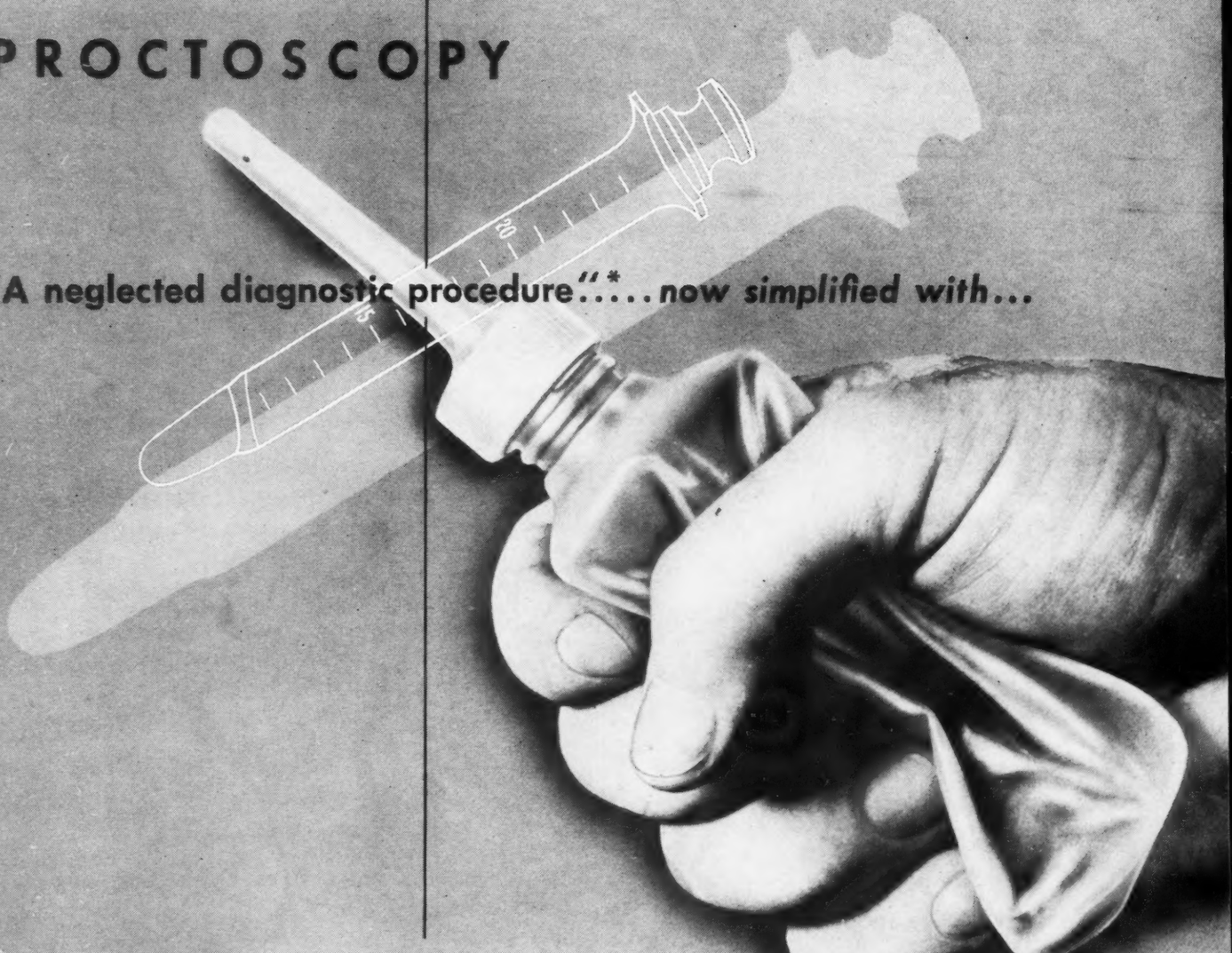
Just one tablet at bedtime of this new combination of NEMBUTAL and Reserpine will calm the worries of most patients with mild anxiety states. Yet, patients have a sense of well-being the next day—keep their drive and energy. The synergistic effect of the combination produces smooth, gentle, prolonged sedation: NEMBUTAL acts quickly to induce drowsiness at bedtime, Reserpine sedation calms the patient through the following day. Small dosage makes side effects rare. Also recommended for treatment of mild essential hypertension. Prescribe NEMBU-SERPIN to give your anxiety patients a sound sleep tonight, a calm day tomorrow. In bottles of 100. Abbott

Each NEMBU-SERPIN Filmtab contains—
NEMBUTAL® Calcium (Pentobarbital Calcium, Abbott), 30 mg. (½ gr.)
and Reserpine, 0.25 mg.

®Filmtab—Film-sealed tablets; pat. applied for.

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THE FLEET ENEMA

DISPOSABLE UNIT

*"Probably no other office procedure except blood pressure determination in the adult gives as high a percentage of positive diagnostic information."
— Jl. La. St. Med. Soc., 106:356, Sept. '54.

It is now a simple matter to prepare patients for proctoscopic or sigmoidoscopic examination during an office visit. The Fleet Enema *Disposable* Unit is superior in cleansing effect to a tap water or saline enema of one or two pints and less irritating than a soap suds enema. Thorough left colon catharsis, with minimal discomfort to the patient, is usually a matter of only four or five minutes.

Each 4½ fl. oz. disposable "squeeze bottle" contains, per 100 cc., 16 gm. sodium biphosphate and 6 gm. sodium phosphate . . . an enema solution of Phospho-Soda (Fleet) . . . gentle, prompt, thorough.

Founded in 1869

"Phospho-Soda", "Fleet" and "Fleet Enema" are registered trade-marks of C. B. Fleet Co., Inc.

C. B. FLEET CO., INC. • LYNCHBURG, VA.

IN THE DETECTION AND MANAGEMENT OF INFLAMMATORY CONDITIONS . . . C·R·P·A

Tests for C-reactive protein depend on a single factor . . . the presence of inflammation.

C·R·P·A

More Accurate than Sedimentation Rate Determinations[1]

"False positives" do not occur in tests for C-reactive protein because this abnormal protein appears only in patients with inflammatory conditions but is never present in normal serum.[2] Disappearance of CRP or changes in its concentration parallel more closely and more promptly variations in the patient's condition than usually evidenced by fluctuations in sedimentation rate.

●

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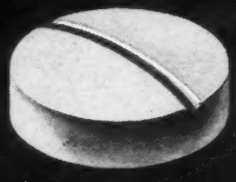
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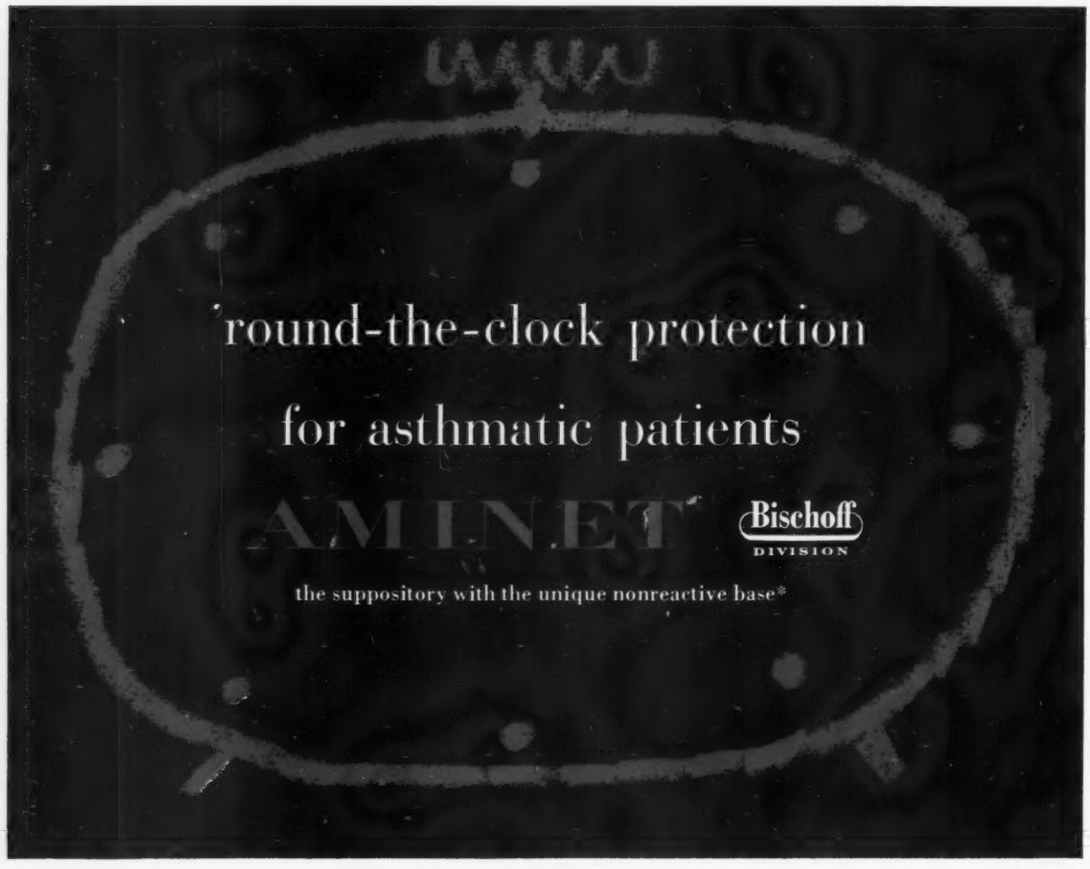
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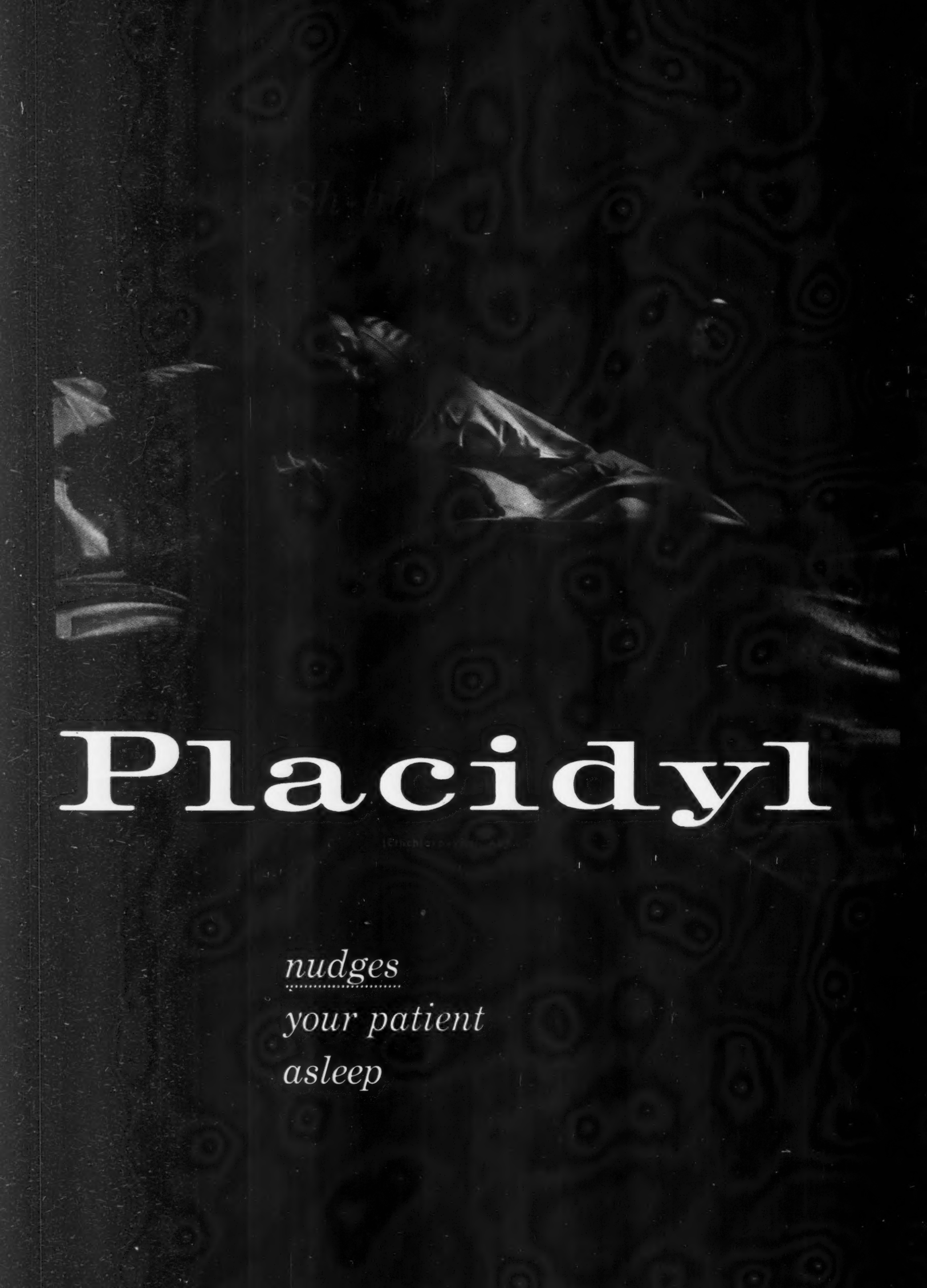
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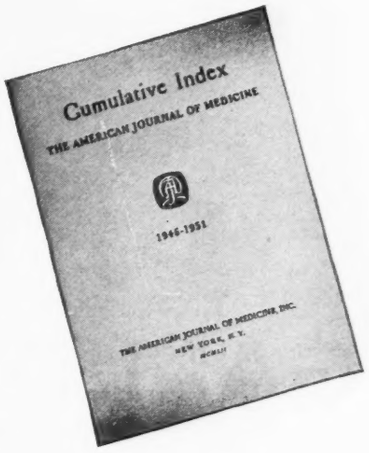
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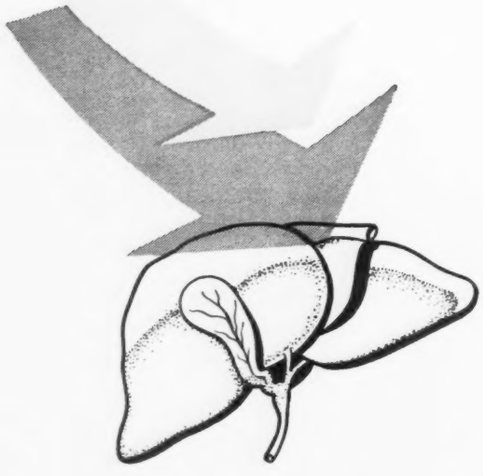
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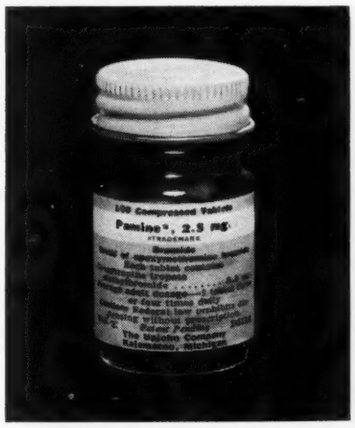
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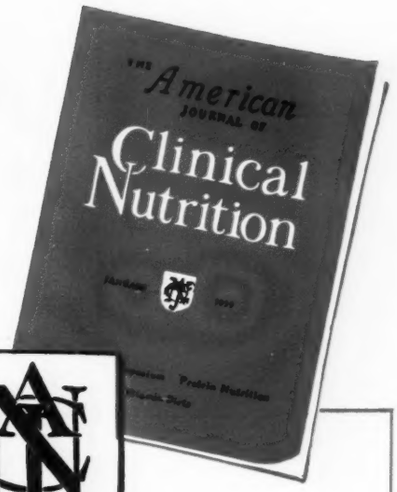
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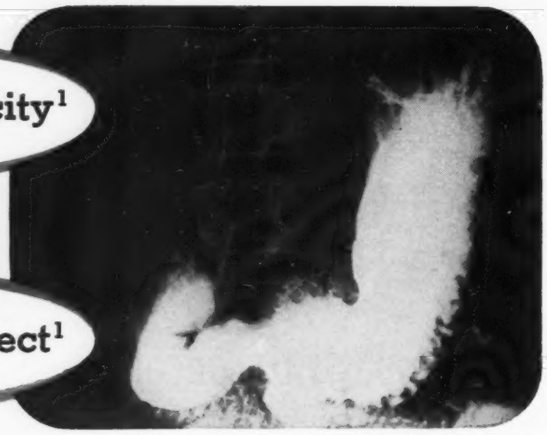
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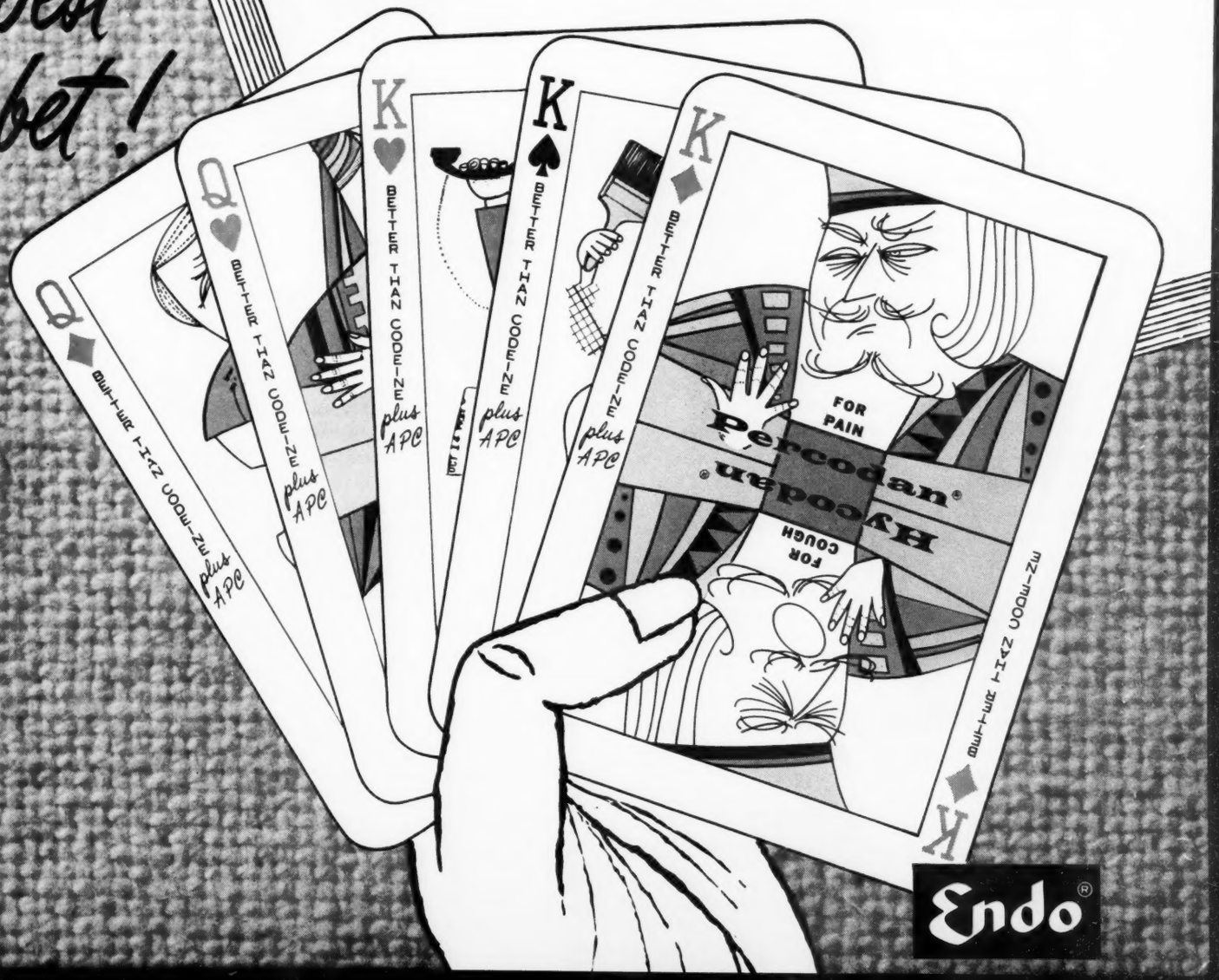
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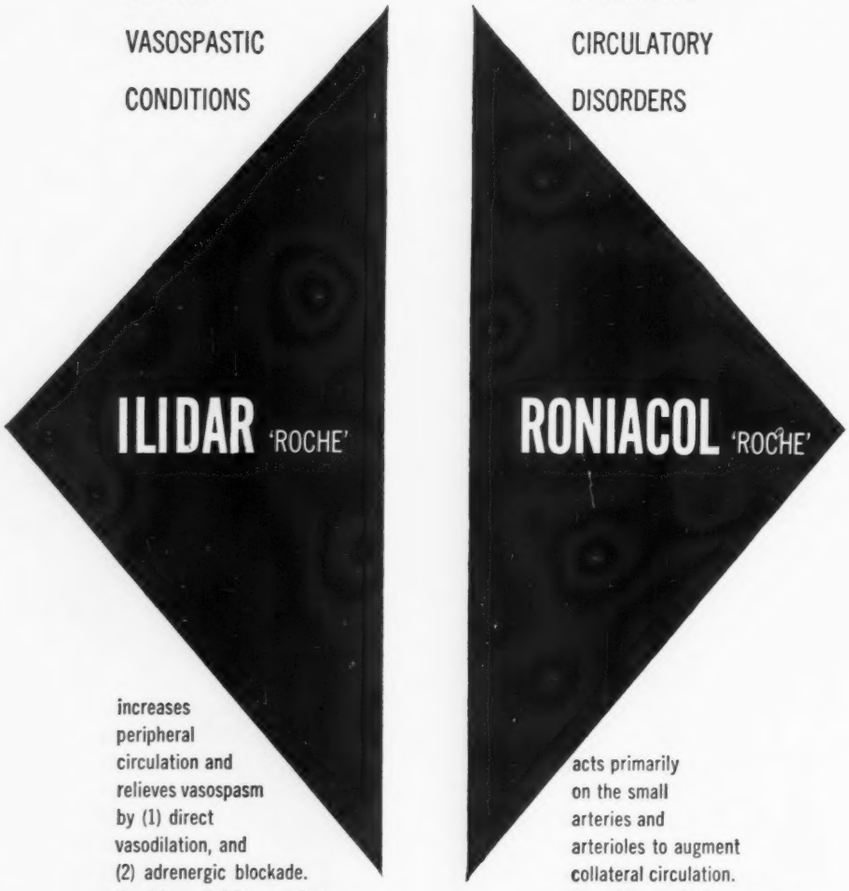
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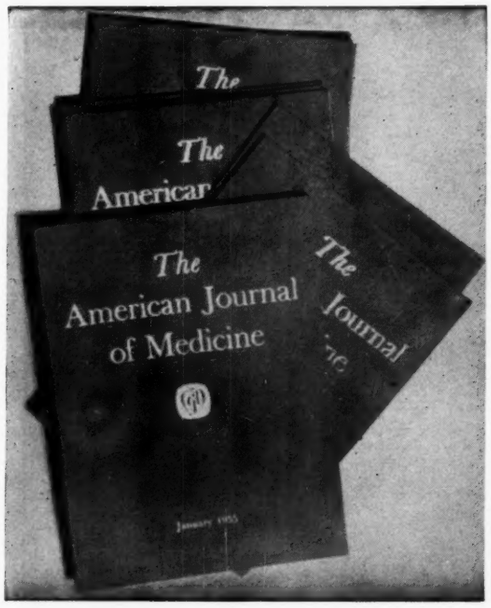


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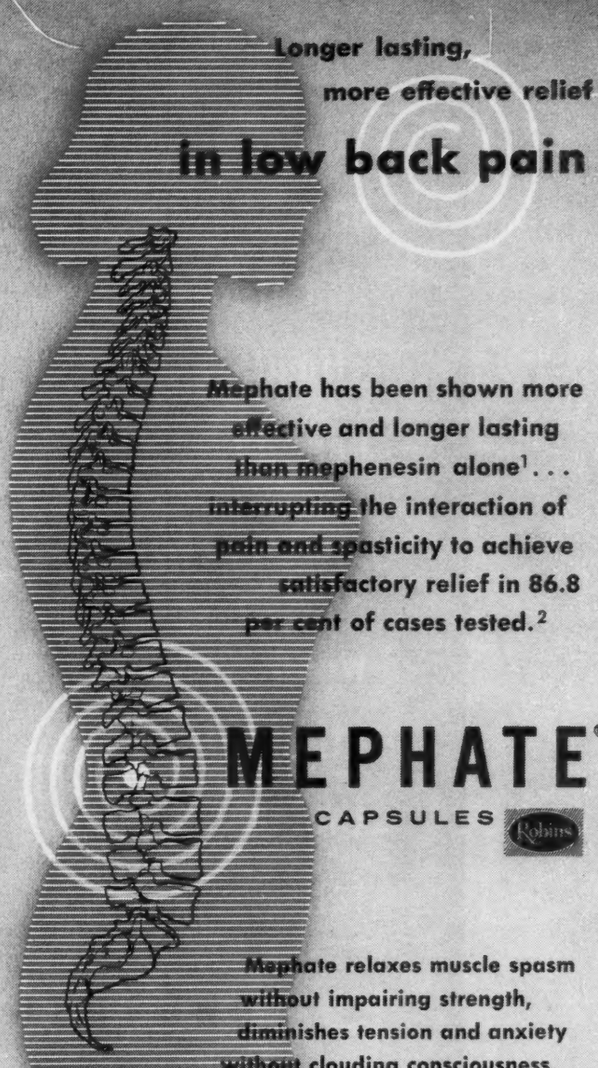
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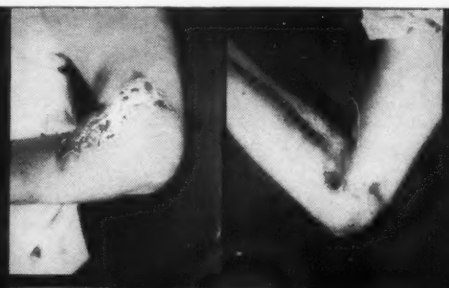
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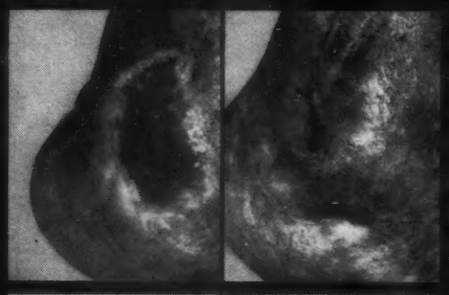


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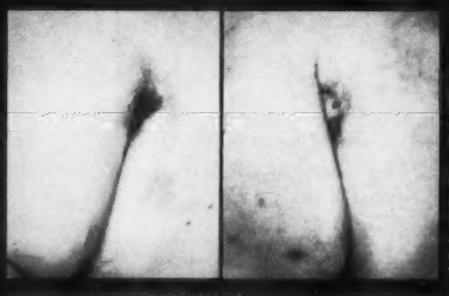
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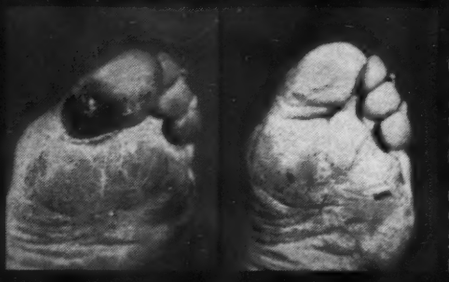
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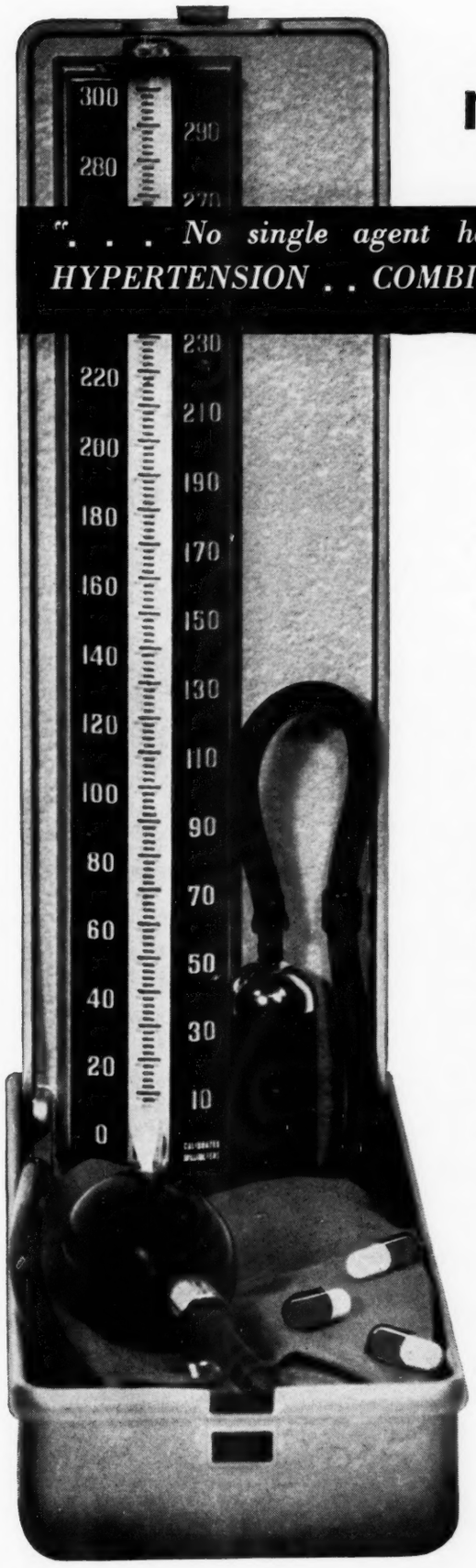


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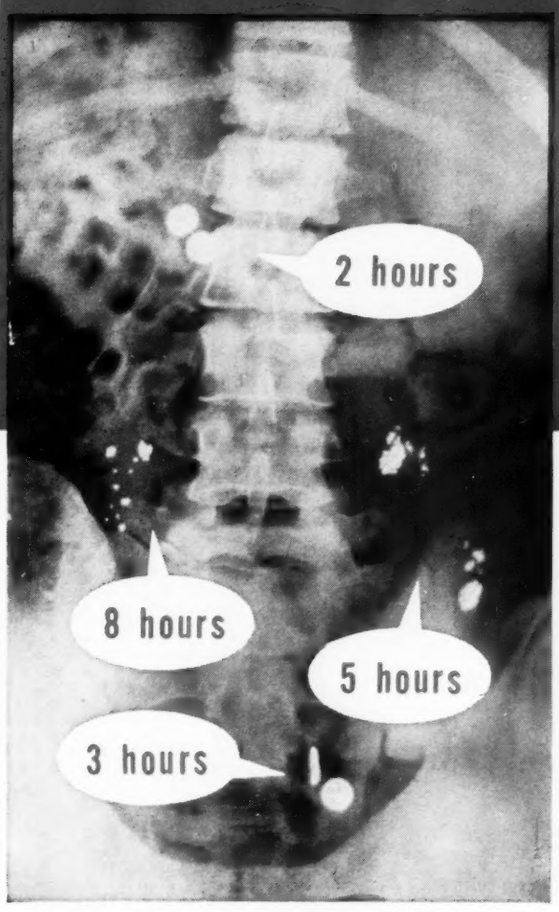
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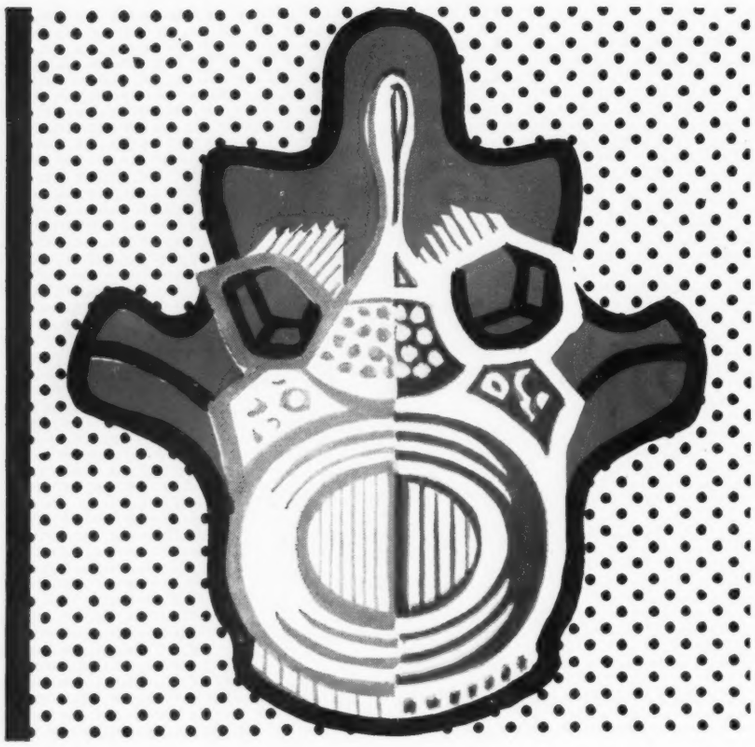
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(1) Payne, R. W.; Shetlar, M. R.; Farr, C. H.; Hellbaum, A. A., and Ishmael, W. K.: J. Lab. & Clin. Med. *45*:331, 1955. (2) Bunim, J. J.; Williams, R. R., and Black, R. L.: J. Chron. Dis. *1*:168, 1955. (3) Holbrook, W. P.: M. Clin. North America *39*:405, 1955.

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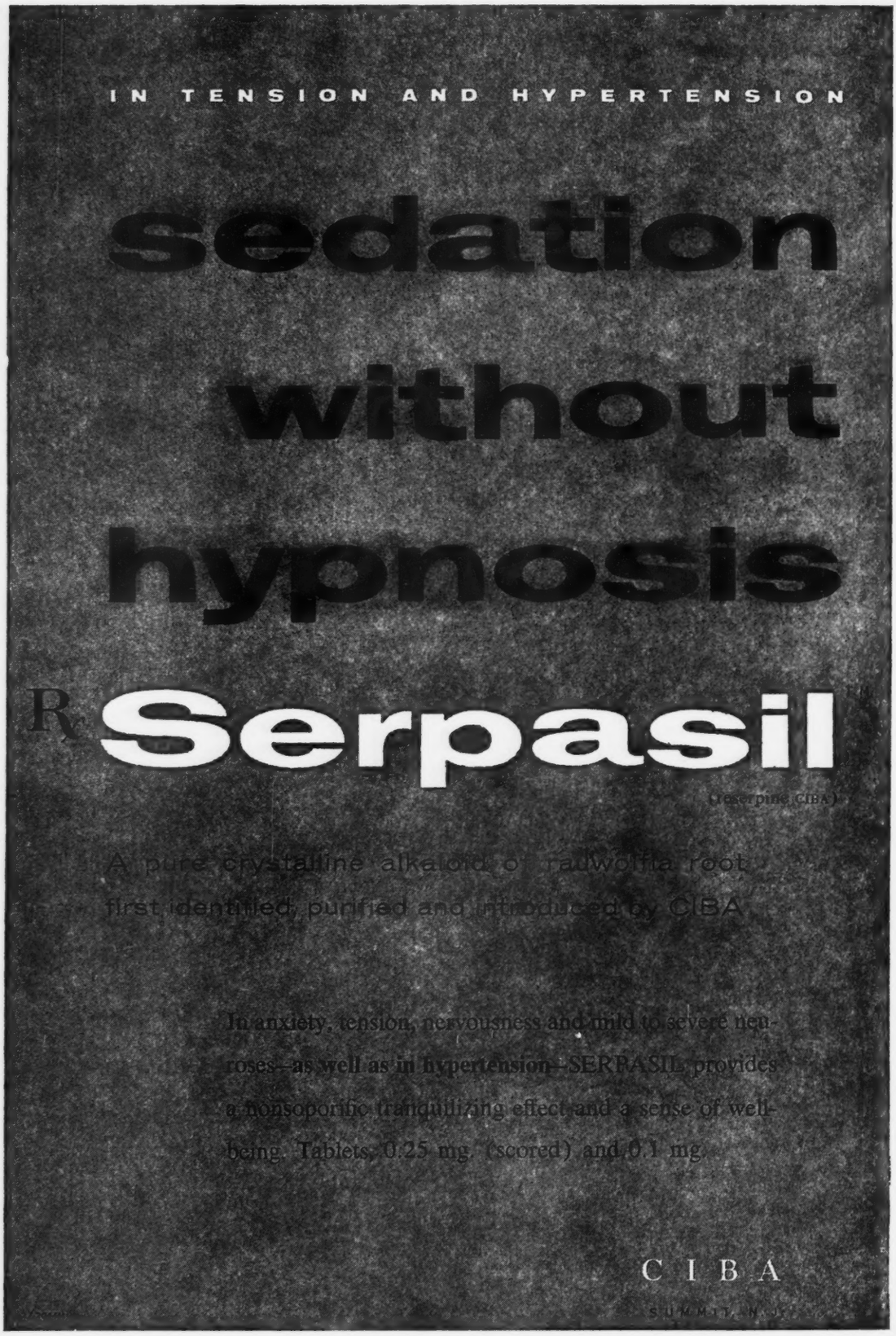
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